

No. 25-1087

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

IN RE:

CENTER FOR BIOLOGICAL DIVERSITY, PEOPLE FOR PROTECTING
PEACE RIVER, BAYOU CITY WATERKEEPER, HEALTHY GULF,
MANASOTA-88, PORTNEUF RESOURCE COUNCIL, RISE ST. JAMES
LOUISIANA, SIERRA CLUB, WATERKEEPER ALLIANCE, and
WATERKEEPERS FLORIDA,

Petitioners.

**APPENDIX OF ATTACHMENTS IN SUPPORT OF
PETITION FOR WRIT OF MANDAMUS**

VOLUME 6 of 7

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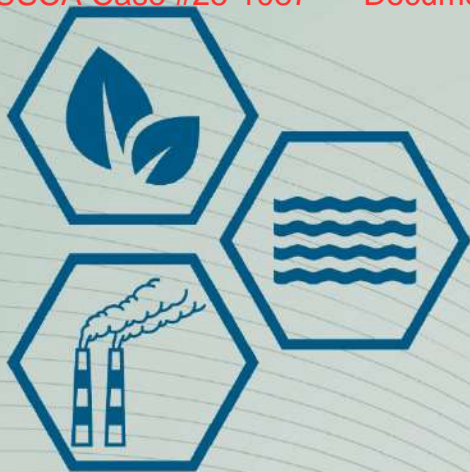
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Toxicological Profile for Lead

August 2020



U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

APPX ATT_V6_2316

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to “...effectuate and implement the health related authorities” of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to “...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances” under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
August 2020	Final toxicological profile released
May 2019	Draft for public comment toxicological profile released
August 2007	Final toxicological profile released
April 1993	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Pb continued to be used as an anti-knock agent in National Association for Stock Car Auto Racing (NASCAR) fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weathered surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989b, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms (see Section 5.4 for a more detailed discussion of the environmental fate of Pb). Particulate matter containing Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils, which limits the rate of leaching. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, tire weights, and imported children's toys, traditional or folk remedies, and candy/food

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packaging. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb is associated with living in areas contaminated by Pb (e.g., soil or indoor dust in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998a; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012). Based on a multimedia Pb exposure modeling analysis for children 1–5 years old at upper percentiles of blood Pb (PbB) levels in the U.S. population, soil and dust ingestion are dominant exposure pathways, but for lower percentiles, other age groups (e.g., younger children), or specific local U.S. locations, the main other exposure sources/ pathways could be important, such as drinking water and food (Zartarian et al. 2017).

PbB has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2015–2016, CDC 2018a, 2019), the geometric mean PbB in a representative sample of U.S. adults, ≥ 20 years old, was 0.920 $\mu\text{g/dL}$ (95% confidence interval [CI] 0.862, 0.982). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.758 $\mu\text{g/dL}$ (95% CI 0.675, 0.850). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2018a; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 µg/dL is associated with adverse effects, particularly in children. PbB levels associated with adverse effects vary by endpoint. Adverse effects occur at PbB <5 µg/dL and for the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤5 µg/dL). CDC (2018b) states that “no safe blood lead level in children has been identified.” As a result, U.S. public health policy has changed to focus on eliminating lead poisoning as a public health problem. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. The current CDC reference value, based on data from the NHANES 2007–2008 and 2009–2010, is 5 µg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤5 µg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves out discussion of effects that may have been observed in animal models that have not been studied in humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of

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exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

Toxic effects of Pb have been observed in every organ system that has been rigorously studied. Clinical significance of some of the organ system effects at low levels of exposure and blood Pb is more substantial than for others (e.g., neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects). This is not surprising because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Adverse health effects have been observed in these systems at PbB ≤ 10 $\mu\text{g/dL}$. Exposure thresholds for effects on specific organ systems have not been identified (i.e., no safe level has been identified). Cognitive deficits in children occurring at the lowest PbBs (≤ 5 $\mu\text{g/dL}$) are the best substantiated effects. However, data for some organ systems results are inconsistent, and insufficient data are available to provide information on dose-response relationships. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies on the health effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer *in utero* and subsequently can continue to absorb maternal Pb from ingestion of breast milk. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2.

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Neurological Effects in Children. Numerous prospective and large cross-section studies in children provide consistent evidence of decrements in neurological function, including decrements in cognitive function (learning and memory), altered behavior and mood (attention, hyperactivity, impulsivity, irritability, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These effects have been associated with a PbB range from ≤ 5 to >50 $\mu\text{g/dL}$, with numerous studies providing evidence for effects at PbB ≤ 5 $\mu\text{g/dL}$. Taken together, studies support the concept that Pb affects cognitive function in children prenatally and/or environmentally exposed to low levels of Pb. No threshold for these effects has been identified (i.e., no safe level has been identified). Decrement in cognitive function increase with PbB, and several PbB-effect models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 $\mu\text{g/dL}$, compared to when PbB increases from levels >10 $\mu\text{g/dL}$. Supra-linear dose-response relationships for neurological outcomes are discussed in greater detail in Section 2.16 (Neurological). At higher PbB (>30 $\mu\text{g/dL}$), other neurotoxic effects have been observed, including alterations in nerve function (decrements in fine and gross motor skills, peripheral neuropathy) and encephalopathy.

Neurological Effects in Adults. Epidemiological studies in adults demonstrate decrements in neurological function associated with PbB. All of the cognitive and neurobehavioral effects of Pb observed in children also have been observed in adults associated with PbB ranging from ≤ 10 to >50 $\mu\text{g/dL}$, with evidence of effects occurring at PbB ≤ 5 $\mu\text{g/dL}$. At higher PbB (>30 $\mu\text{g/dL}$), other observed neurotoxic effects include peripheral neuropathy, psychiatric symptoms (depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia), and changes in regional brain volumes and neurochemistry. It is not clear if cognitive decrements are related to exposures that occurred during adulthood or during periods of nervous system development (e.g., prenatal and childhood exposures) or if effects are due to cumulative exposure. Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible impact of exposures on childhood to adult outcomes.

Renal Effects. Adverse renal effects of Pb are well-established in numerous epidemiological studies. Studies show consistent evidence of renal damage and reduced renal function associated with a wide range of PbB (≤ 10 – 50 $\mu\text{g/dL}$), with several studies providing evidence for effects at PbB ≤ 5 $\mu\text{g/dL}$. Deficits in renal function include enzymuria, proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate (GFR). At higher PbB (>30 $\mu\text{g/dL}$), Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, interstitial fibrosis,

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and tubular necrosis. Note that Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality). In addition, other causes of decreased renal function could result in an increased body burden of Pb.

Cardiovascular Effects. A large number of epidemiological studies in adults show adverse cardiovascular effects associated with a PbB range from ≤ 5 to >50 $\mu\text{g/dL}$. Effects on blood pressure is the most-studied cardiovascular outcome, with studies showing increased systolic and diastolic blood pressure, with some evidence of effects occurring at $\text{PbB} \leq 5$ $\mu\text{g/dL}$. A few studies show increased blood pressure in children and pregnant women. Nawrot et al. (2002) estimated that with doubling of PbB (for example, from 5 to 10 $\mu\text{g/dL}$), systolic and diastolic blood pressure would increase by 1 and 0.6 millimeters of mercury, respectively. Other cardiovascular effects include increased risk of hypertension and heart disease, atherosclerosis, altered cardiac conduction, cardiac disease, and increased mortality due to cardiovascular disease. A recent study concluded that low-level environmental Pb exposure is an important risk factor for cardiovascular disease mortality (Lanphear et al. 2018).

Hematological Effects. The toxicity of Pb to the hematological system of humans has been established in numerous studies in adults and children. Exposure to Pb causes dose-dependent decreases in heme synthesis through inhibition of the enzyme delta-aminolevulinic acid dehydratase (δ -ALAD). At $\text{PbB} \leq 10$ $\mu\text{g/dL}$, decreased blood hemoglobin is observed; however, it should be noted that the magnitude of this decrease is typically small and may not represent a biologically significant change. As PbB increases, further decreases in blood hemoglobin and loss of erythrocytes due to a Pb-induced increased membrane fragility results in the development of anemia (NAS 2013). Other effects of Pb on the hematological system include decreased activity of other erythrocyte enzymes (pyrimidine 5'-nucleotidase or red blood cell membrane $\text{Ca}^{2+}/\text{Mg}^{2+}\text{ATPase}$) and altered levels of plasma erythropoietin (a hormone that stimulates red blood cell formation); however, fewer studies on these endpoints have been published and study results are mixed.

Immunological Effects. Epidemiological studies provide evidence that Pb exposure can perturb the immune systems of children and adults. Evidence for this derives from changes in various indicators of humoral and cell-mediated immunity in association with increasing PbB. Effects have been observed in populations that had average $\text{PbB} < 10$ $\mu\text{g/dL}$. These effects are consistent with more extensive studies conducted in animal models and isolated immune cells that have shown that Pb can perturb the humoral and cell-mediated immune systems, leading to sensitization, autoimmunity, and inflammation (EPA 2014c; NAS 2013).

Reproductive Effects in Males. Health effects of Pb on the male reproductive system have been evaluated in numerous epidemiological studies. Effects include damage to sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm), possible alterations in serum levels of reproductive hormones (testosterone, estradiol, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), decreased fertility, and histopathological changes to the testes. Severity of these effects increases with PbB. Studies conducted in populations with mean PbB ≤ 10 $\mu\text{g/dL}$ provide evidence of damage to sperm, although effects are more consistently observed at PbB > 10 $\mu\text{g/dL}$. Regarding effects on serum levels of reproductive hormones, results of available studies for PbB ranging from ≤ 10 to > 50 $\mu\text{g/dL}$ are inconsistent; thus, Pb-induced effects on circulating reproductive hormones are not firmly established. At higher PbB (> 10 $\mu\text{g/dL}$), a few studies provide evidence of more severe effects, including decreased fertility and histopathological damage to testes.

Reproductive Effects in Females. Compared to studies of male reproductive effects, the epidemiologic literature database for effects of Pb on the female reproductive system is smaller, with most epidemiological studies conducted in populations with mean PbB ≤ 10 $\mu\text{g/dL}$. Studies provide some evidence of alterations in serum reproductive hormone levels (estradiol, LH, and FSH), decreased fertility, increased spontaneous abortion, increased preterm birth, and earlier age at onset of menopause. However, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects.

Developmental Effects (Excluding Neurodevelopmental). Numerous epidemiological studies have evaluated developmental outcomes, with most studies conducted in populations with maternal and/or umbilical cord PbB ≤ 10 $\mu\text{g/dL}$. Some studies provide evidence of decreased birth size (weight, length, head circumference), decreased child growth (weight, height, head circumference, trunk length, leg length, arm length, body mass index [BMI]), and delayed onset of puberty in males and females. Although it is difficult to assess dose-dependence for developmental effects within the relatively narrow range of PbB (≤ 10 $\mu\text{g/dL}$) in most studies, dose-related decreases in birth weight have been observed in populations with PbB ≤ 10 $\mu\text{g/dL}$. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent and several studies, including prospective studies, show no associations with non-neurodevelopmental outcomes.

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Other Health Effects Associated with Pb. In addition to the effects summarized above, health effects to other organ systems have been reported. The epidemiological databases for these effects are much less extensive than for the effects reviewed above. Effects described below occur over a wide range of PbBs, including $\text{PbB} \leq 10 \mu\text{g/dL}$. However, results for most endpoints are inconsistent and insufficient data are available to provide information on dose-response relationships.

- **Respiratory Effects.** Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease).
- **Endocrine Effects (Excluding Reproductive Hormones).** Studies in adults, adolescents, and children show effects on thyroid function, cortisol levels, vitamin D levels, and serum levels of growth factors. Effects on thyroid function are the most studied effect, although results do not demonstrate a consistent pattern of effect.
- **Hepatic Effects.** Most studies were conducted in workers with $\text{PbB} > 10 \mu\text{g/dL}$. Several studies show altered plasma levels of liver enzymes, although no consistent pattern of effects has been observed. Liver enlargement and increased gall bladder wall thickness have been associated with PbB.
- **Musculoskeletal Effects.** Studies provide evidence of bone loss, increased markers of bone metabolism/turn over, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries) in adults and children.
- **Gastrointestinal Effects.** Gastrointestinal colic is a predominant clinical symptom of acute Pb poisoning. Epidemiological studies provide evidence of gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from $8 \mu\text{g/dL}$ to approximately $100 \mu\text{g/dL}$. However, most studies are survey or cross-sectional studies of small populations of workers.
- **Body Weight Effects.** A few studies evaluating effects of $\text{PbB} \leq 10 \mu\text{g/dL}$ on body weight provide some evidence of decreased body weight in children and adults, although inconsistent results have been reported.
- **Ocular Effects (Excluding Neurological Effects).** Limited data provide some evidence that exposure to Pb is associated with macular degeneration in adults and increased risk of cataracts.

Cancer. Numerous epidemiological studies have evaluated associations between Pb exposure and cancer. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent, with several negative studies, and interpretation of data may be limited due to confounding

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factors (e.g., smoking status, family history of cancer, co-exposure to other carcinogens). At PbB ≤ 10 $\mu\text{g/dL}$, increased risks were reported for all cancers and lung cancer. At PbB >10 $\mu\text{g/dL}$, increased risks were observed for all cancer, respiratory tract cancer, stomach cancer, intestinal cancer, cancer of the larynx, and glioma.

The Department of Health and Human Services classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). In 1988, EPA classified Pb as a probable human carcinogen based on sufficient evidence in animals; evidence in humans was considered inadequate (IRIS 2004). The International Agency for Research on Cancer (IARC) has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006).

1.3 MINIMAL RISK LEVELS (MRLs)

As reviewed in Section 1.2, epidemiological studies have evaluated the health effects of Pb in all organ systems. For the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤ 5 $\mu\text{g/dL}$). Because the lowest PbBs are associated with serious adverse effects (e.g., declining cognitive function in children), MRLs for Pb have not been derived.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of lead (Pb). It contains descriptions and evaluations of epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others identify potential health effects in persons with elevated PbB, the information in this section is organized by health effect.

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of epidemiology studies included in this chapter of the profile.

Since development of the 2007 Toxicological Profile on Lead (ATSDR 2007), results of numerous epidemiological studies have prompted growing attention to the adverse health effects of Pb exposures that result in blood Pb concentrations (PbB) of $<10 \mu\text{g/dL}$ (EPA 2014c). Awareness of the potential adverse consequences of such exposures has led to changes in U.S. public health policy, with a focus on eliminating lead poisoning as a public health problem (CDC 2012d; EPA 2016b). In 2012, CDC accepted their Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) recommendation to establish a PbB reference value for Pb, replacing the $10 \mu\text{g/dL}$ level of concern. The reference value is based on the 97.5th percentile of the PbB distribution among children 1–5 years of age in the United States, using data generated by NHANES (CDC 2012d). At that time, the PbB reference was approximately $5 \mu\text{g/dL}$ (NHANES 2007–2010) (CDC 2018a). ACCLPP recommended that the reference value be updated every 4 years using the two most recent NHANES cycles and would be used in recommendations for follow-up evaluations and identification of high-risk childhood populations (CDC 2012d). It is likely that PbB values among children will continue to decline; therefore, the primary focus of this toxicological profile is on health effects associated with low Pb exposure (i.e., those observed at $\text{PbB} \leq 5 \mu\text{g/dL}$). Detailed information on effects at $\text{PbB} \leq 10 \mu\text{g/dL}$ is also presented to examine potential

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exposure-response relationships. Information on health effects observed at higher PbB levels (>10 µg/dL) is also included to provide a comprehensive overview of the adverse effects of Pb.

Literature Search Strategy. The literature on health effects of Pb in humans is enormous, with countless epidemiological studies in workers and the general population, including children. Due to the extent of the Pb database in humans, it is impossible to cite all, or even most, of the studies on health effects of Pb; thus, this profile does not attempt to provide a comprehensive review of all literature; instead, the profile summarizes the major lines of epidemiological evidence regarding health effects in humans. Although the literature database on adverse effects of Pb in laboratory animals is also extensive, given the large number of studies available in humans, animal studies are not included in this toxicological profile. For a recent review of studies in animal models, the reader should consult the EPA's Integrated Science Assessment for Lead (EPA 2014c).

The following were used as primary sources to identify literature on health effects of Pb:

- The previous Toxicological Profile for Lead (ATSDR 2007) was used to identify literature published through 2007.
- The EPA (2014c) Integrated Science Assessment for Lead was used to identify literature published from 2006 to 2013.
- Literature searches were conducted from 2013 to 2019 to identify studies published after EPA (2014c).

In addition, recent reviews by NTP (2012) and NAS (2013) were consulted. As anticipated, the literature search revealed an extensive epidemiological database of literature published since 2013. To narrow the evaluation to those studies of greatest utility identifying health effects of low exposures to Pb, a series of inclusion criteria were defined; only studies meeting the criteria were considered for inclusion in the toxicological profile. These criteria are described further in Appendix B. Data from selected studies were tabulated and discussed in subsequent sections of this chapter.

Duration of Exposure. Typically, toxicological profiles organize the discussion of health effects according to exposure duration categories. However, this is not a particularly informative approach to the discussion of Pb epidemiology. The epidemiologic study of Pb toxicity in human populations has relied on internal dose metrics (e.g., PbB, bone Pb) for evaluating associations between health outcomes. These metrics are considered to represent relatively recent exposure history, in the case of PbB, and longer-term

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cumulative exposure, in the case of CBLI or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in Pb exposure over time (including peak exposure periods that may have occurred in the past), and, in general, the complete exposure history is not known. Health outcomes associated with acute exposures is available from clinical case studies of Pb poisoning (see Section 2.2). However, even in these cases, the exposure duration that preceded the identification of the case is rarely known with certainty.

Routes of Exposure. For the general population, exposure to Pb occurs primarily via the oral route, with some contribution from the inhalation route, whereas inhalation exposures can be more important in occupational settings, depending on particle size. In addition, occupational exposure to organic Pb compounds may involve dermal absorption as a significant exposure route. This profile does not attempt to separate health effects by route of exposure. As noted previously, epidemiology studies have relied on internal dose metrics (e.g., PbB, bone Pb), which reflect Pb body burden (to varying degrees), irrespective of the route of exposure. The primary systemic toxic effects of Pb are the same regardless of the route of entry into the body,

Exposure Metric. To quantify exposure in humans, data are expressed in terms of absorbed Pb, and not in terms of external exposure levels (e.g., concentration in water) or dose (e.g., mg/kg/day). The most common metric of absorbed dose for Pb is the concentration of lead in blood (PbB), although other measures of exposure (e.g., concentration of Pb in bone, hair, teeth, or urine) are used; however, measurements of Pb in urine, teeth, and hair are not as reliable as measurements in blood or bone. PbB mainly reflects exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (see Section 3.1). Pb in bone is considered a biomarker of cumulative or long-term exposure because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Most of the body burden of Pb (the total amount of Pb in the body) is distributed to the bone, with approximately 94 and 76% of the body burden found in bone in adults and children, respectively. The remainder is distributed to blood and soft tissues. However, the concentration of Pb in blood can vary considerably with age and physiology/lifestage (e.g., pregnancy, lactation, menopause). For this reason, measurement of Pb in bone has seen wider application in epidemiological studies of adults in which measures of cumulative lifetime exposures are of interest. However, bone Pb measurements require specialized radiologic equipment (e.g., K-shell x-ray fluorescence; XRF) and, as a result, are used less commonly than PbB in human epidemiology. Since most of the epidemiology has relied on PbB as the dose metric, this profile has focused on describing dose-response relationships based on PbB to facilitate comparisons across studies and endpoints. This

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approach also aligns with public health practices, which rely on PbB for evaluating elevated exposures to Pb (CDC 2012d; EPA 2016b). However, it is recognized that some health outcomes may be correlated with cumulative exposure, in which case, bone Pb may be a better dose metric than PbB. For these outcomes, short-term variation in PbB may contribute to exposure classification error (i.e., the same PbB could be observed in individuals who have different bone Pb). The exposure history of the subjects may also be an important factor in determining associations observed between outcomes and blood or bone Pb. Some studies of historically exposed occupational populations (e.g., former workers) have found stronger associations between bone Pb and health outcomes than with PbB, while some studies of concurrently exposed populations have found stronger associations with PbB (Shih et al. 2007).

Confounding Factors and Effect Modifiers. Bias can occur in epidemiological studies when the background risk of the outcome being measured is not the same in the exposed and reference groups. Confounders are variables that affect the measured outcome and are also associated with the Pb exposure metric (e.g., PbB, bone Pb). For example, Pb body burden increases with age; therefore, age can be a confounding factor if it is also a risk factor for the outcome (e.g., renal or cardiovascular disease). Not adjusting for confounders may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on whether it is a negative or positive confounding variable. Effect modifiers are variables that affect the measured outcome independently of the Pb exposure metric. For example, renal disease from any cause can affect blood pressure and, thereby, could interact with Pb to change blood pressure. Effect modifiers can also be confounders, if they are associated with the Pb exposure metric (e.g., socio-economic status [SES] and cognitive development). Recall bias may also contribute to uncertainties and should be considered as a confounding factor. For example, interviews of parents are a standard method for estimating potential co-variables that might affect child development in prospective studies, as there are no alternatives for studies in children. Thus, inaccurate recall may potentially influence study outcomes. Failure to account for important effect modifiers can result in underestimation or overestimation of the apparent strength of the association, depending on the direction of the effect of the modifying variable. Confounding factors and effect modifiers are discussed in greater detail in sections that describe specific categories of health effects. Epidemiological studies provide information about the strengths of statistical associations between exposure metrics (e.g., blood Pb) and health outcomes. However, statistical associations do not necessarily reflect causal associations. Evidence for causal associations can include demonstration of exposure-response relationships, occurrence of the outcome or its precursors in controlled studies conducted in experimental models (*in vivo* and *in vitro*), and consistency of observed statistical associations with known modes of action of Pb.

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Overview of Health Effects of Pb. The health effects of Pb are diverse, and exposure to Pb is associated with toxicity to every organ system. This is not surprising because the mechanisms of action associated with Pb-induced toxicity, including perturbations of ion homeostasis and transport, protein binding, oxidative stress, and inflammation, are common to all cell types. In addition, Pb is widely distributed throughout the body, and has been measured in all tissues evaluated (see Section 3.1.2). For all organ systems, toxicity has been observed at PbB ≤ 10 $\mu\text{g/dL}$. Neurological effects of Pb are of greatest concern because effects are observed in infants and children; furthermore, these effects may result in life-long decrements in neurological function. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The weight-of-evidence for all adverse health effects is strongly supported by studies in animal models and *in vitro* systems; see EPA (2014c) for a review of this literature.

Effects observed in association with PbB are briefly described below. Note that for some of the effects listed below, study results are not consistent, which limits interpretation of observations; this is reviewed in more detail in subsequent sections for each organ system in Chapter 2. The most extensive epidemiological databases examining Pb are for neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects.

- **Neurological Effects:**

- **Children.** Decreased cognitive function; altered mood and behaviors that may contribute to learning deficits, altered neuromotor and neurosensory function, peripheral neuropathy, and encephalopathy.
- **Adults.** Decreased cognitive function including attention, memory, and learning; altered neuromotor and neurosensory function; altered mood and behavior; and decreased peripheral nerve conduction velocity.

- **Renal Effects.** Decreased GFR, proteinuria, enzymuria, impaired tubular transport, and histopathological damage.

- **Cardiovascular Effects.** Increased systolic and diastolic blood pressure, increased risk of hypertension, atherosclerosis, altered cardiac conduction, increased risk of heart disease, and increased mortality due to cardiovascular disease.

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- **Hematological Effects.** Inhibition of δ -ALAD leading to decreased blood hemoglobin and anemia, decreased activity of other erythrocyte enzymes, and altered plasma erythropoietin (EPO) levels.
- **Immunological Effects.** Perturbation of humoral and cell-mediated immune systems, decreased resistance to disease, sensitization, autoimmunity, and inflammation.
- **Reproductive Effects:**
 - **Males.** Effects on sperm, alterations in semen quality, decreased fertility, histopathological damage to the testes, and possible altered serum concentrations of reproductive hormones.
 - **Females.** Possible alterations in serum concentrations of reproductive hormones, decreased fertility, spontaneous abortion, preterm birth, and earlier age at the onset of menopause.
- **Developmental Effects.** Decreased birth weight and size, decreased anthropometric measures in children, and delayed onset of puberty in males and females.

Other health outcomes associated with PbB include the following:

- **Respiratory Effects.** Decreased lung function, increased bronchial hyperreactivity, increased risk of asthma, and obstructive lung disease.
- **Hepatic Effects.** Possible increases in plasma liver enzymes and cholesterol, enlarged liver, and increased thickness of gall bladder wall.
- **Endocrine Effects.** Possible alterations in serum of thyroid hormones, altered cortisol responses, alteration in serum growth factors, and decreased serum vitamin D levels.
- **Gastrointestinal Effects.** Abdominal pain/colic, nausea, vomiting, and diarrhea and/or constipation.
- **Musculoskeletal Effects.** Bone loss, osteoporosis, dental caries, tooth loss, and periodontitis.

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- **Ocular Effects.** Possible macular degeneration and cataracts.
- **Cancer.** Increased risk of cancer, including all cancers, cancer of the respiratory tract, intestinal tract, and larynx, and glioma.

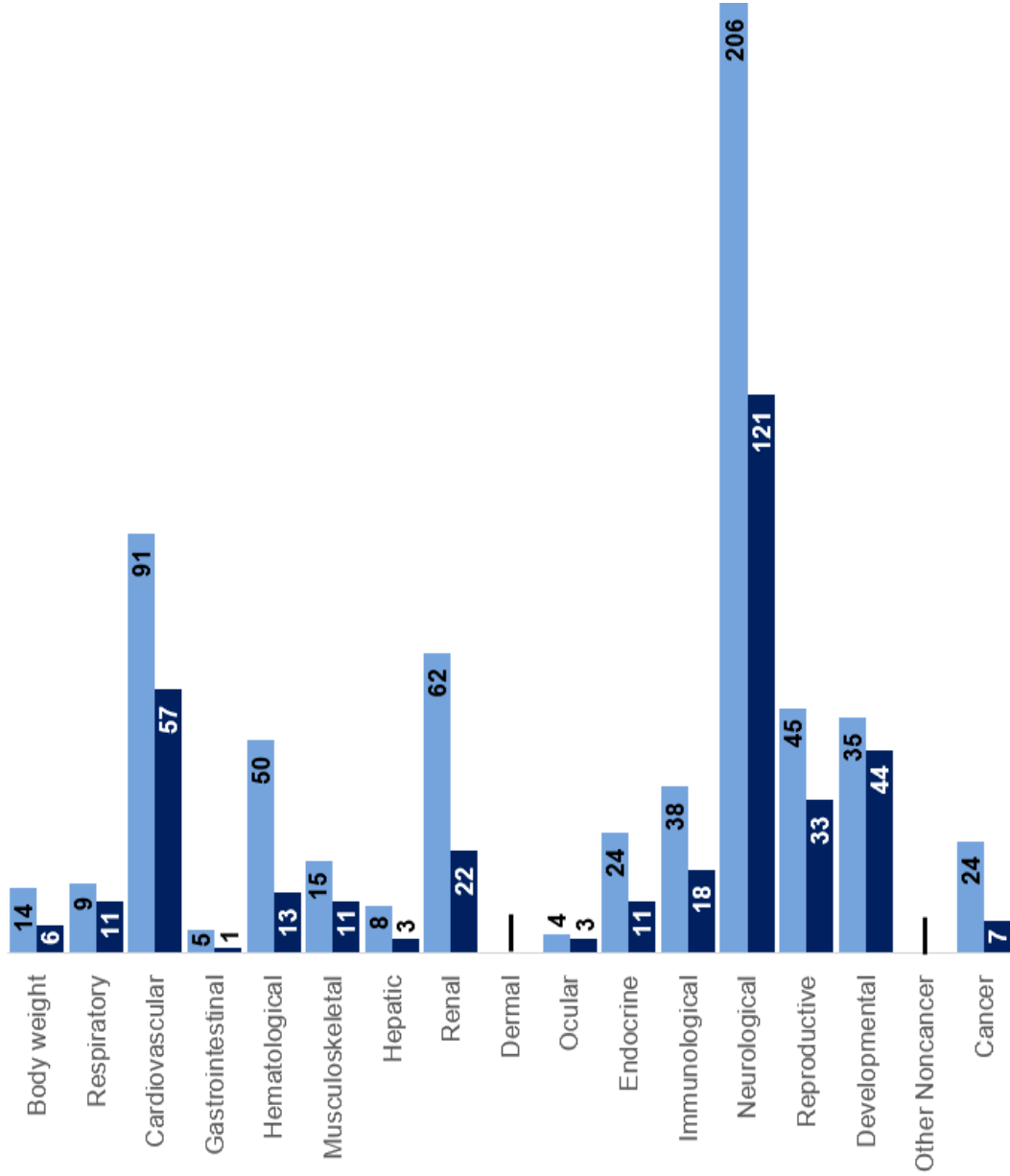
Many specific health effect endpoints have been evaluated in numerous studies. To provide the reader with a weight-of-evidence for these endpoints, the profile indicates if results are consistent and corroborated in numerous studies or if results are inconsistent (or mixed).

Figure 2-1 shows the numbers of epidemiological studies included in this chapter of the toxicological profile, based on health outcome studied. The number of studies evaluating effects at $\text{PbB} \leq 10 \mu\text{g/dL}$ also is indicated. The $\text{PbB} \leq 10 \mu\text{g/dL}$ was selected to evaluate effects at the lowest PbB (e.g., $\leq 5 \mu\text{g/dL}$) and to evaluate potential exposure-response relationships for $\text{PbB} \leq 10 \mu\text{g/dL}$. As noted above, due to the enormous number of epidemiological studies published, the profile does not attempt to provide a comprehensive review of all literature. Therefore, this figure should not be interpreted as depicting all epidemiological studies that have been published on Pb toxicity.

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Figure 2-1. Overview of the Number of Studies Examining Associations Between PbB and Health Effects^a

Most studies examined the potential cardiovascular, renal, and neurological effects of lead. A subset of studies evaluating health effects for **PbB ≤10 µg/dL** compared to **all PbB studies** (counts represent studies examining endpoint)



^aIncludes studies discussed in Chapter 2. A total of 694 epidemiological studies (including those finding no effect) have examined toxicity; some studies examined multiple endpoints.

2.2 ACUTE LEAD TOXICITY

Overview. No controlled studies in humans have evaluated the acute toxicity of Pb (acute Pb poisoning). Available information is anecdotal, obtained from numerous case reports. Thus, data are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Acute Pb toxicity is characterized by symptoms of abdominal pain/colic, vomiting, constipation, peripheral neuropathy, and cerebral edema and encephalopathy, which can lead to seizures, coma, and death. Children are more susceptible than adults to acute Pb poisoning. Additional information on toxicity of ingested Pb debris (e.g., Pb shot) is provided in Appendix C.

Rather than reviewing numerous case reports, the information presented below was taken from the following reviews: Beers et al. (1999); Chisolm (1977); Klaassen (2001); Landrigan (1995); NAS (1972); Needleman (2004); and Skerfving and Bergdahl (2015). Citations are only specifically noted below if quantitative information is discussed.

Confounding Factors, Effect Modifiers, and Uncertainties. There are several uncertainties from case reports on acute toxicity of Pb. Therefore, it is difficult to establish dose-response relationships for acute toxicity relative to PbB. Uncertainties include:

- Baseline PbB data are rarely available.
- There is a lack of quantitative data on the dose of Pb ingested.
- No information on the fractional absorption of ingested Pb.
- Time from ingestion of Pb to development of symptoms of acute Pb toxicity is often unknown.
- Time from ingestion of Pb to first clinical evaluation and PbB assessment is often unknown.
- Gastrointestinal symptoms and general malaise are typically the first symptoms of acute Pb toxicity to appear; these general symptoms are often attributed to other causes, leading to an initial misdiagnosis or delay in diagnosis.
- Data to develop PbB time-concentration curves are incomplete.
- Numerous factors may contribute to individual susceptibility to acute Pb exposure, including age, intercurrent illness, underlying developmental issues, dietary and nutritional status, concurrent medication use, and exposure to other chemicals.

Clinical Presentation of Acute Pb Toxicity. The onset of acute toxicity is rapid, usually occurring within 1–5 days of exposure. The main organ systems involved are the gastrointestinal, hematological, and

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neurological systems. Signs and symptoms increase in severity with increasing PbB, ranging from mild to severe. Gastrointestinal effects include abdominal colic/pain, nausea, vomiting, diarrhea, and constipation. Massive loss of gastrointestinal fluids can lead to dehydration. Hematological effects include decreased hemoglobin synthesis, anemia, and acute hemolytic crisis characterized by anemia and hemoglobinuria. Numerous neurological symptoms are associated with acute Pb toxicity, including headache, hyperirritability, decreased activity, paresthesia, muscle pain and weakness, ataxic gait, decreased consciousness, cerebral edema leading to seizures and coma, encephalopathy, and death. Other reported symptoms include astringency of the mouth, metallic taste in the mouth, and thirst.

Susceptibility of Children. Children are more susceptible than adults to Pb poisoning because the fractional absorption of ingested Pb is higher than in adults and the developing central nervous system is more vulnerable to toxicity compared to a fully developed nervous system (Needleman 2004). In addition to being more sensitive than adults, acute toxicity in children may have long-lasting effects. For example, children who recover from acute encephalopathy can have long-term decreases in cognitive abilities, attention deficits, and impaired behavior. Children are also susceptible due to increased exposure.

Dose-Response Relationship for Acute Toxicity Relative to PbB. As noted above, data from case reports are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Some general observations can be made from available reports; however, dose-response relationships are highly uncertain and may not apply to individuals acutely exposed to Pb. At PbB <30 µg/dL, signs and symptoms of acute toxicity typically are not observed. This should not be interpreted to mean that no Pb-induced adverse effects (e.g., decreased hemoglobin synthesis) occur at PbB <30 µg/dL, but that symptoms causing individuals to seek medical intervention (e.g., abdominal colic and vomiting) typically are not observed at PbB <30 µg/dL. As PbBs increase to >30 µg/dL, signs and symptoms of gastrointestinal and neurological toxicity are observed, with severity increasing with PbB. Pb-induced encephalopathy has been reported at PbB <100 µg/dL, but is more commonly associated with PbB >100 µg/dL (NAS 1972). In a review of 96 cases of death due to acute Pb poisoning in children, death occurred at PbB >100 µg/dL (NAS 1972).

2.3 DEATH

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and death. Studies include exposure of workers and general populations, and report a wide range of PbB levels. In the general population, studies have shown significant associations between PbB and mortality

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due to disease of blood and blood-forming organs. In occupationally exposed individuals, mortality due to infection, endocrine diseases, and digestive diseases were associated with PbB in male workers, but not female workers, while mortality due to respiratory disease was associated with PbB in a cohort of male workers. In addition, studies of the general population and Pb occupations show an association between PbB and cumulative “all-cause” mortality (including cancer). However, results are inconsistent and interpretation may be limited due to confounding factors. Studies assessing associations between PbB and mortality due to cardiovascular diseases and cancer are discussed in Sections 2.5 and 2.19, respectively, and are not reviewed here.

The following causes of death have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in a few studies with generally consistent results.
- > 10 $\mu\text{g/dL}$:
 - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in several studies with positive associations in some studies.
 - Increased risk of death from chronic or unspecified nephritis or non-malignant kidney disease; evaluated in several studies with positive associations in some studies.
 - Increase risk of death from infection; demonstrated in one study.
 - Increased risk of death from endocrine disease; demonstrated in one study.
 - Increased risk of death from digestive disease; evaluated in several studies with positive associations in some studies.
 - Increased risk of death from diseases of the blood and blood forming organs; demonstrated in one study.
 - Increased risk of death from respiratory diseases (emphysema, pneumonia, and other respiratory diseases); evaluated in several studies with positive associations in some studies.

Confounding Factors and Effect Modifiers. Numerous factors can influence results of epidemiological studies evaluating associations between Pb exposure and mortality, including age, sex, BMI, ethnicity, poverty level, education, alcohol consumption, smoking status, hypertension, diabetes, family history of diseases, activity level, total cholesterol, postmenopausal status, nutritional status, and co-exposure with other metals (i.e., arsenic or cadmium). Failure to account for these factors may attenuate or strengthen

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the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Measures of Exposure. Studies examining the association between Pb exposure and mortality evaluate exposure by measurement of PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and mortality. Studies of general populations and workers are briefly summarized in Table 2-1. In the general population, at PbB ≤ 10 $\mu\text{g/dL}$, a positive dose-response relationship was suggested for all-cause mortality and mortality due to coronary heart disease (Khalil 2009, 2010; Menke et al. 2006; Schober et al. 2006), although Weisskopf et al. (2009) did not show an increased risk for all-cause mortality. At >10 $\mu\text{g/dL}$, results of occupational exposure and general population studies are mixed and do not establish a pattern of effects or exposure-response relationships. In the general population, findings of the Lustberg and Silbergeld (2002) study suggested dose-response for PbB and all-cause mortality. In Pb workers, a dose-effect relationship was observed for all-cause mortality and mortality due to endocrine disease, infection, and digestive disease (Chowdhury et al. 2014; Kim et al. 2015), although Malcolm and Barnett (1982) did not observe a dose-effect relationship between Pb and all-cause mortality in Pb battery workers.

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Table 2-1. Summary of Epidemiological Studies Evaluating Death^a

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects ^b
PbB ≤10 µg/dL			
Cheung et al. 2013	Mean: 4.44	All-cause mortality ^c	OR: 1.045 (1.013 1.079)*
Cross-sectional study; n=3,482 (NHANES III)			
Khalil 2010; Khalil et al. 2009	Quintiles	All-cause mortality ^c	HR Q1 (reference) HR Q2: 0.80 (0.45, 1.42) HR Q3: 0.70 (0.39, 1.24) HR Q4: 0.60 (0.34, 1.06) HR Q5: 1.20 (0.69, 2.09) p-trend=0.905
Prospective cohort study; n=533 women (age 65–87 years)	<ul style="list-style-type: none"> • Q1: <4 • Q2: 4 • Q3: 5 • Q4: 6–7 • Q5: >7 		Spline for 5th knot: p=0.009* Wald test: p=0.0843
Khalil et al. 2009	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All-cause mortality ^c	Adjusted HR ≥8 µg/dL: 1.59 (1.02, 2.49); p=0.041*
Prospective cohort study; n=533 women (age 65–87 years)		All-cause mortality excluding deaths due to cancer and cardiovascular disease	Adjusted HR ≥8 µg/dL: 1.22 (0.48, 3.10); p=0.673
Menke et al. 2006	Mean: 2.58 Tertiles:	All-cause mortality ^c	Adjusted HR T1 (reference) T2: 0.91 (0.72, 1.15) T3: 1.25 (1.04, 1.51)* p-trend=0.002*
Longitudinal study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	<ul style="list-style-type: none"> • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.63 		
Neuberger et al. 2009	5.8	Tuberculosis	SMR: 0.0 (0.0, 10.80)
Retrospective cohort study; mortality data from Oklahoma State Department of Health; 1999–2001		Bronchitis, emphysema, asthma	SMR: 1.10 (0.863, 13.84)
		Kidney disease	SMR: 0.984 (0.573, 1.576)
Schober et al. 2006	Tertiles	All-cause mortality ^c	RR T2: 1.24 (1.05, 1.48)* RR T3: 1.59 (1.28, 1.98)*; p-trend<0.001
Longitudinal study; n=9,757 (NHANES III; age ≥40 years)	<ul style="list-style-type: none"> • T1: <5; mean 2.6 • T2: 5–9; mean 6.3 • T3: >10; mean 11.8 		

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Table 2-1. Summary of Epidemiological Studies Evaluating Death^a

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects ^b
Weisskopf et al. 2009	Mean (SD): 5.6 (3.4)	All-cause mortality ^c	Adjusted HR
Longitudinal study; n=868 men (Normative Aging Study; age 21–80 years)	Tertiles: • T1: <4 • T2: 4–6 • T3: >6		• T1: 1 (reference) • T2: 0.99 (0.71, 1.37) • T3: 1.01 (0.71, 1.44) • p-trend=0.92
PbB >10 µg/dL			
Barry and Steenland 2019	Q1: 0–<5 Q2: 5–<25 Q3: 25–<40 Q4: ≥40	All-cause mortality ^c	HR Q4: 1.38 (1.24, 1.53)*
Retrospective study; n=58,368 male workers (10-year follow-up of Chowdhury et al. 2014)	T1: 0–<25 T2: 25–<40 T3: ≥40	Chronic obstructive pulmonary disease	HR Q4: 1.46 (0.94, 2.28)
		Chronic renal disease	HR T3: 1.81 (0.91, 3.57)
		Cerebrovascular disease (stroke)	SMR Q4: 0.73 (0.58, 0.91)
		Ischemic heart disease	SMR Q4: 0.70 (0.63, 0.77)
Chowdhury et al. 2014	Quartiles • Q1: 0–<5 • Q2: 5–<25 • Q3: 25–<40 • Q4: ≥40	All-cause mortality ^c	SMR Q4: 0.80 (0.75, 0.84)* SMR overall: 0.69 (0.66, 0.71)
Survey study; n=58,368 male workers (mean age 38.9 years)		Chronic obstructive pulmonary disease	SMR Q4: 0.86 (0.64, 1.12) SMR overall: 0.65 (0.54, 0.78)
		Chronic renal disease	SMR Q4: 1.01 (0.58, 1.64) SMR overall: 0.65 (0.44, 0.93)
Cooper 1988; Cooper et al. 1985	Mean • Battery (n=1326): 62.7 • Smelters (n=537): 79.7	Nonmalignant respiratory disease	Battery PMR: 0.90 (0.74, 1.10) Smelter PMR: 0.76 (0.53, 1.11)
Cohort study; n=4,519 battery workers; 2,300 smelters		Cirrhosis of the liver	Battery PMR: 1.29 (0.96, 1.73) Smelter PMR: 0.63 (0.35, 1.15)
		Chronic or unspecified nephritis	Battery PMR: 2.06 (1.26, 3.18)*; p<0.01 Smelter PMR: 1.86 (0.80, 3.66)
		Chronic nephritis	Battery PMR: 1.48 (0.88, 2.49) Smelter PMR: 1.20 (0.50, 2.86)

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Table 2-1. Summary of Epidemiological Studies Evaluating Death^a

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects ^b
Kim et al. 2015	Mean	All-cause mortality ^c	Males: RR T3: 1.36 (1.03, 1.79)*; p<0.05 Females: RR T3: 1.30 (0.41, 4.16)
Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	<ul style="list-style-type: none"> • Males: 8.8 • Females 5.8 Tertiles: <ul style="list-style-type: none"> • T1: <10 • T2: 10–20 • T3: >20 	Non-malignant death	Males: RR T3: 0.95 (0.56, 1.51) Females RR T3: 0.99 (0.13, 7.19)
		Infection	Males: RR T2: 3.73 (1.06, 13.06)*; p<0.05 Females: not reported
		Endocrine disease	Males: RR T3: 4.25 (0.90, 20.04)*; p<0.1 Females: not reported
		Respiratory disease	Males: RR T2: 1.46 (0.28, 7.49) Females: RR T2: 3.49 (0.31, 39.05)
		Digestive disease	Males: RR T3: 3.23 (1.33, 7.86)*; p<0.05 Females: RR T2: 3.66 (0.33, 40.70)
Lundstrom et al. 1997	Mean:	All-cause mortality ^c	Total cohort SMR: 0.9 (0.8, 1.0)
Retrospective cohort study; n=3,979 workers	<ul style="list-style-type: none"> • In 1950: 62.2 • In 1987: 33.2 	Respiratory disease	Total cohort SMR: 0.4 (0.2, 0.8)
		Digestive organs	Total cohort SMR: 0.6 (0.3, 1.1)
Lustberg and Silbergeld 2002	Tertiles:	All-cause mortality ^c	RR T2: 1.17 (0.90, 1.52) RR T3: 1.46 (1.14, 1.86)*
Longitudinal study; n=4,292; age 30–74 years (NHANES II)	<ul style="list-style-type: none"> • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29 		
Malcolm and Barnett 1982	Group1 (non-occupational exposed); not reported Group 2: (light occupational Pb exposure); mean 57 Group 3: (high occupational Pb exposure); not reported	All-cause mortality ^c	Group 3 SMR: 1.07; p=0.134
Retrospective cohort study; n=754 Pb battery workers			

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Table 2-1. Summary of Epidemiological Studies Evaluating Death^a

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects ^b
McDonald and Potter 1996	Mean 113	Diseases of the blood and blood forming organs	SMR: 9.68 (1.95, 28.28)*
Prospective cohort study; n=454 pediatric patients diagnosed with Pb poisoning, Massachusetts, 1923–1966, followed through 1991; age of diagnosis <1–9 years		Nervous-system and sense-organ diseases	SMR: 2.86 (0.57, 8.35)
		Respiratory diseases	SMR: 1.95 (0.78, 4.02)
		Pneumonia	SMR: 2.10 (0.68, 4.90)
		Digestive system diseases	SMR: 1.37 (0.44, 3.21)
		Genitourinary system diseases	SMR: 1.69 (0.02, 9.43)
		Chronic nephritis	SMR: 5.00 (0.06, 27.82)
		All-cause mortality ^c	SMR: 1.74 (1.40, 2.15)*
McElvenny et al. 2015	Mean: 44.3 Range: 2.3–321.5	All-cause mortality ^c	Males: SMR 1.10 (1.06, 1.14)* Females: SMR 1.00 (0.91, 1.09) Total SMR: 1.09 (1.05, 1.12)*
Cohort study; n=9,122 workers; mean age 29.2 years		Respiratory system diseases	Males: SMR: 1.17 (1.06, 1.30)* Females: SMR: 1.24 (0.98, 1.57) Total SMR: 1.18 (1.08, 1.30)*
		Digestive system diseases	Males: SMR: 1.22 (1.03, 1.45)* Females: SMR: 0.84 (0.52, 1.35) Total SMR: 1.16 (0.99, 1.36)
		Genitourinary diseases	Males: SMR: 1.02 (0.72, 1.44) Females: SMR: 0.67 (0.28, 1.60) Total SMR: 0.95 (0.69, 1.31)
		Non-malignant kidney disease	Males: SMR: 1.30 (0.76, 2.24) Total SMR: 1.29 (0.79, 2.11)

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Table 2-1. Summary of Epidemiological Studies Evaluating Death^a

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects ^b
Selevan et al. 1985	Mean: 56.3	All tuberculosis	SMR: 1.39 (0.69, 2.49)
Retrospective cohort study; n=1,987 male workers		Diseases of the central nervous system	SMR: 0.84 (0.61, 1.12)
		Diseases of the respiratory system	SMR: 1.25 (0.92, 1.66)
		Other respiratory diseases	SMR: 1.87 (1.28, 2.64)*
		Diseases of the digestive system	SMR: 0.51 (0.26, 0.89)
		Diseases of the genitourinary system	SMR: 0.93 (0.42, 1.77)
		Chronic and unspecified nephritis and other renal sclerosis	SMR: 1.92 (0.88, 3.64)
		All other	SMR: 0.88 (0.67, 1.14)
		All-cause mortality ^c	SMR: 1.07 (1.00, 1.14)*
		Non-malignant respiratory disease	SMR: 1.44 (1.16, 1.77)*
		Emphysema	SMR: 2.20 (1.45, 3.20)*
Steenland et al. 1992	Mean: 56.3	Pneumonia and other respiratory disease	SMR: 1.88 (1.34, 2.56)*
		Acute kidney disease	SMR: 0.91 (0.02, 5.07)
		Chronic kidney disease	SMR: 1.26 (0.54, 2.49)
		All-cause mortality ^c	HR T1: 1.15 (1.10, 1.21)*
		Stroke	HR T1: 1.24 (1.03, 1.50)*
Steenland et al. 2017	Median: 26 Tertiles: • T1: 20-<30 • T2: 30-<409 • T3: >40	Ischemic heart disease	HR T1: 1.14 (1.04, 1.26)*
		Chronic obstructive pulmonary disease	HR T1: 1.43 (1.10, 1.86)*
		Chronic kidney disease	HR T3: 1.54 (0.77, 3.08)
Cohort study; n=88,187 Pb workers (United States n=58,313, United Kingdom n=9,122, Finland n=20,752)			

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Table 2-1. Summary of Epidemiological Studies Evaluating Death^a

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects ^b
Wong and Harris et al. 2000	Mean:	All-cause mortality ^c	SMR: 1.045 (1.012, 1.08)*; p<0.01
Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	<ul style="list-style-type: none">• All workers: 64.0• Battery workers: 62.7• Smelters: 79.7		

^aStudies assessing death due to cardiovascular disease and cancer are discussed in Sections 2.5 and 2.19, respectively.

^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

^cIncludes cancer and/or cardiovascular deaths.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PbB = blood lead concentration; PMR = proportionate mortality ratio; RR = rate ratio or relative risk; SD = standard deviation; SMR = standard mortality ratio

2.4 BODY WEIGHT

Overview. Compared to other health effect endpoints, there is little information on Pb exposure and body weight measures. However, a few epidemiological studies have evaluated effects of Pb exposure on body weight in children, adolescents, and adults. The studies reviewed below focused on effects at PbB ≤ 10 $\mu\text{g/dL}$. Inverse associations have been observed between PbB and BMI, and decreased risks of being overweight or obese have been reported. However, some studies did not observe associations and one study reported a positive association between PbB and the risk of obesity in women.

Note that studies evaluating the effects of exposure to Pb on birth weight are reviewed in Section 2.18 (Developmental).

The following effects on body weight have been associated with PbB ≤ 10 $\mu\text{g/dL}$:

- Decreased BMI and risk of being overweight or obese in children and adolescents; observed in a few studies.
- Decreased BMI and risk of being overweight or obese in adults; not corroborated.
- Increased risk of obesity in women; not corroborated.

Measures of Exposure. Most studies evaluating effects of chronic Pb exposure on body weight evaluate exposure by measurement of PbB. A few other studies examining associations between Pb exposure and body weight used Pb concentration in urine, bone, and/or dentin as biomarkers of exposure; however, these studies did not report PbB (Kim et al. 1995; Liu et al. 2019a; Padilla et al. 2010; Shao et al. 2017).

Confounding Factors and Effect Modifiers. Numerous factors contribute to body weight (or BMI), including age, sex, race, nutrition, diet, daily activity level, intercurrent illness, genetic pre-disposition for body type, income level, education, and alcohol and tobacco use. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

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Effects at Blood Pb Levels $\leq 10 \mu\text{g/dL}$. Results of studies evaluating effects of PbB $\leq 10 \mu\text{g/dL}$ on body weight are briefly summarized in Table 2-2 and an overview of results is provided in Table 2-3; study details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 1. Studies have been conducted in children and adolescents (Burns et al. 2017; Cassidy-Bushrow et al. 2016; Hauser et al. 2008; Scinicariello et al. 2013) and adults (Scinicariello et al. 2013; Wang et al. 2015). The largest study evaluating associations between PbB and body weight is a study of children, adolescents, and adults participating in NHANES, 1999–2006; this study included adjustments for numerous confounding factors (see the *Supporting Document for Epidemiological Studies for Lead*, Table 1) (Scinicariello et al. 2013). In children and adolescents (n=10,693), results show an inverse association between PbB and BMI-Z score and risk of being overweight or obese. In a smaller study in children (n=131), inverse associations were observed between PbB and BMI and BMI-Z score (Cassidy-Bushrow et al. 2016). Other studies in small populations of boys showed no associations between weight, BMI and/or BMI-Z score (Burns et al. 2017; Hauser et al. 2008). Results of studies in adults are mixed. The largest study in adults (n=15,899) shows inverse associations between PbB and BMI and risk of being overweight and obese, with a negative trend (p-trend: ≤ 0.01) over quartiles (Scinicariello et al. 2013). No association was observed between PbB and BMI in a small study on women (n=107) (Ronco et al. 2010) or a larger study in men (n=2235) (Wang et al. 2015). In contrast, the risk of being obese was increased in a large population (n=3323) of women (Wang et al. 2015). Thus, except for the Wang et al. (2015) study, available studies show either no association or an inverse association between PbB $\leq 10 \mu\text{g/dL}$ and body weight and/or BMI.

Mechanisms of Action. The mechanisms involved in the development of Pb-induced changes in body weight have not been established. However, alterations of the hypothalamic-pituitary-adrenal axis, stress-induced elevations in glucocorticoid levels, oxidative stress, and altered lipid metabolism have been proposed (reviewed by Scinicariello et al. 2013; Shao et al. 2017; Wang et al. 2015).

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Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^b
Burns et al. 2017	Median 3.0	HT-Z score	Adjusted β (95% CI), HT-Z score per unit lnPbB: -0.26 (-0.40, -0.13); $p < 0.001^*$
Prospective cohort of 481 Russian boys enrolled at age 8–9 years and followed until age 18 years		BMI-Z score	Adjusted β (95% CI), BMI-Z score per unit lnPbB: -0.14 (-0.31, 0.04); $p = 0.12$
Cassidy-Bushrow et al. 2016	Mean (SD): 2.45 (2.53)	BMI	Adjusted RR (95% CI) for BMI $\geq 85^{\text{th}}$ percentile 0.57 (0.33, 0.98); $p = 0.041^*$
Birth cohort of 131 children, 2–3 years of age		BMI-Z score	Adjusted β (95% CI) for BMI Z-score: -0.35 (-0.60, -0.10); $p = 0.012^*$
Hauser et al. 2008	Mean: 3	Weight	Adjusted β (95% CI), per unit log-PbB: -0.761 (-1.54, 0.02); $p = 0.067$
Cross-sectional study of 489 boys, 8–9 years of age		BMI	Adjusted β (95% CI), per unit log-PbB: -0.107 (-0.44, 0.23); $p = 0.53$
Ronco 2010	Median	BMI	No differences in PbB were observed between BMI categories
Cross-sectional study of 107 women of childbearing age (median age: 27 years) from Chile; data collection period not reported	<ul style="list-style-type: none"> All: 1.0 Low weight: 1.7 Normal weight: 2.3 Overweight: 1.0 		

2. HEALTH EFFECTS

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Scinicariello et al. 2013	Gmean (SE)	BMI-Z score	Adjusted β (SE) (BMI Z-score per PbB quartile):
Cross-sectional study of children and adolescents (n=10,693; age 3–19 years) adults (n=15,899, age ≥20 years) using NHANES data (1999–2006)	• Children/adolescents: 1.12 (0.02)	BMI-Z score (children and adolescents)	• Q3: −0.15 (0.06); p=0.01*
	• Adults: 1.59 (0.02)		• Q4: −0.33 (0.07); p ≤ 0.01*
	• Quartiles (all):		• p-trend: ≤0.01*
	◦ Q1: ≤0.70		Adjusted OR for Q4: 0.67 (0.52, 0.88)*
	◦ Q2: 0.71–1.09		Adjusted OR
◦ Q3: 1.10–1.60	• Q3: 0.70 (0.54, 0.90)*		
	◦ Q4: ≥1.61	Obesity (children and adolescents)	• Q4: 0.42 (0.30, 0.59)*
		BMI (adults)	Adjusted β (SE) (BMI per quartile):
			• Q2: −0.90 (0.20); p ≤ 0.01*
			• Q3: −1.41 (0.22); p ≤0.01*
			• Q4: −2.58 (0.25); p ≤0.01*
			• p-trend: ≤0.01*
		Overweight (adults)	Adjusted OR for Q4: 0.79 (0.65–0.95)*
		Obesity (adults)	Adjusted OR
			• Q2: 0.76 (0.66–0.87)*
			• Q3: 0.66 (0.56–0.77)*
			• Q4: 0.42 (0.35–0.50)*

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Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Wang et al. 2015	PbB:	BMI	β (SE) per PbB quartile
Cross-sectional study of 5,558 adults (men: 2,235, ages 39–65 years; women: 3,323, ages 40–65 years) from 16 locations in China	Men		• Men
	• Median: 4.40		○ Q4: 0.01 (0.20)
	• Quartiles:		○ p-trend: 0.82
	○ Q1: ≤29.00		• Women
	○ Q2: 29.01–44.00		○ Q4: 0.59 (0.17); p<0.05*
	○ Q3: 44.01–62.16		○ p-trend: <0.001*
	○ Q4: ≥62.17		
	Women:	Overweight	Adjusted OR
	• Median: 3.78		• Men
	• Quartiles:		○ Q4: 0.95 (0.72, 1.26)
	○ Q1: ≤25.13		○ p-trend: 0.74
	○ Q2: 25.14–37.79		• Women
	○ Q3: 37.80–54.35		○ Q4: 1.16 (0.92, 1.46)
	○ Q4: ≥54.36		○ p-trend: 0.07
		Obesity	Adjusted OR
			• Men
			○ Q4: 0.88 (0.48, 1.61)
			○ p-trend: 0.99
			• Women
			○ Q4: 1.86 (1.16, 2.98)*
			○ p-trend: <0.01*

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 1 for more detailed descriptions of studies.^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

BMI = body mass index; BMI-Z = BMI z-scores; CI = confidence interval; Gmean = geometric mean; HT-Z = height z-scores; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; SD = standard deviation; SE = standard error

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Table 2-3. Effects on Body Weight Associated with Mean Blood Lead Concentrations (PbBs) $\leq 10 \mu\text{g}^a$

Mean PbB ($\mu\text{g/dL}$)	Population (n) ^b	Weight	BMI	BMI-Z score	Overweight	Obese	Reference
3.0	C (481 boys)	–	–	0	–	–	Burns et al. 2017
2.45	C (131)	–	↓	↓	–	–	Cassidy-Bushrow et al. 2016
3	C (489 boys)	0	0	–	–	–	Hauser et al. 2008
1.0	A (107 women)	–	0	–	–	–	Ronco et al. 2010
1.12	C, Ad (10,693) ^c	–	–	↓	↓	↓	Scinicariello et al. 2013
1.59	A (15,899) ^c	–	↓	–	↓	↓	Scinicariello et al. 2013
4.40	A (2,235, men)	–	0	–	0	0	Wang et al. 2015
3.78	A (3,323, women)	–	0	–	0	↑	Wang et al. 2015

^a↑ = increased; ↓ = decreased; 0 = no change; – = not assessed.

^bUnless otherwise specified, study was conducted in males and females.

^cParticipants from the National Health and Nutrition Examination Survey 1999–2006.

A = adults; Ad = adolescents; BMI = body mass index; BMI-Z = BMI z-scores; C = children

2.5 RESPIRATORY

Overview. Few epidemiological studies have evaluated respiratory effects associated with exposure to Pb; those that are available include cross-sectional studies in adults and prospective and cross-sectional studies in children. Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, increased number and severity of symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). Although most studies found associations between respiratory effects and PbB, other studies did not observe associations.

The following respiratory effects have been associated with PbB:

- $\leq 10 \mu\text{g/dL}$:
 - Decreased lung function; corroborated in a few studies, including studies in children.
 - Increased bronchial hyperreactivity.
 - Increased risk of asthma and obstructive lung disease; evaluated in a few studies with mixed results.

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- >10 µg/dL:
 - Decreased lung function.
 - Symptoms of respiratory disease (e.g., shortness of breath).
 - Increased risk/prevalence of asthma; evaluated in a few studies with mixed results.

Measures of Exposure. Studies evaluating the association between respiratory effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. The etiology for most respiratory diseases is multifactorial; therefore, several factors may contribute to clinical findings. Factors that may contribute to the development of respiratory diseases include poor housing conditions, exposure to allergens (e.g., pet dander, seasonal allergies), exposure to tobacco smoke and other respiratory irritants, and asthma compounded by obesity (Ali and Ulirk 2013). In addition, Aligne et al. (2000) reported that children living in urban settings have an increased risk of asthma. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. General trends for studies showing a relationship between PbB and respiratory effects are shown in Table 2-4. Compared to other toxicological endpoints (e.g., neurological or cardiovascular effects), few studies have evaluated adverse respiratory effects associated with PbB. Data are from cross-sectional studies in adults (Bagci et al. 2004; Bener et al. 2001; Chung et al. 2015; Min et al. 2008a; Pugh Smith and Nriagu 2011; Rokadia and Agarwal 2013), and prospective (Joseph et al. 2005; Rabinowitz et al. 1990) and cross-sectional (Wells et al. 2014) studies in children. Over a range of PbBs that includes PbB ≤10 µg/dL and PbB >50 µg/dL, studies provide evidence for effects in Pb workers compared to controls or associations between PbB and decreased pulmonary function tests indicative of obstructive pulmonary disease (forced expiratory volume in 1 second [FEV₁], FEV₁/forced vital capacity [FVC] ratio, forced expiratory flow at 25–75% of FVC [FEF_{25–75}]), increased bronchial hyperreactivity (indicative of asthma), symptoms of respiratory disease (cough, shortness of breath), and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). With the exception of a prospective study in children, which showed no increased risk of asthma at umbilical cord PbB ≥10 µg/dL compared to <10 µg/dL (Rabinowitz et al. 1990), studies showed positive associations between PbB and respiratory effects.

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Table 2-4. Overview of Respiratory Effects in Adults and Children Chronically Exposed to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Decreased lung function	Chung et al. 2015; Leem et al. 2015; Little et al. 2017; Zeng et al. 2017
	Increased bronchial responsiveness	Min et al. 2008a
	Lung disease (asthma and obstructive lung disease)	Joseph et al. 2005; Rokadia and Agarwal 2013; Wang et al. 2017a; Wells et al. 2014; Zeng et al. 2016
>10–30	Lung disease (asthma)	Pugh Smith and Nriagu 2011
>30–50	Decreased lung function	Bagci et al. 2004
>50	Symptoms of lung disease (phlegm)	Bener et al. 2001
	Lung disease (asthma)	Bener et al. 2001

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating respiratory effects of PbB ≤10 µg/dL are summarized in Table 2-5, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies show associations between PbB ≤10 µg/dL and decreased lung function, increased bronchial hyperreactivity, and increased risk of asthma; findings are consistent with obstructive lung disease. In a cross-sectional study in adults from China with mean PbB of 2.50 µg/dL, an inverse association was observed for the FEV₁/FVC ratio in a population; results are consistent with obstructive airway disease (Chung et al. 2015). In a large pooled cross-sectional study, Korean adults showed a decrease in the FEV₁/FVC ratio in the highest exposure quartile (Leem et al. 2015). A small study in children with a mean PbBs of 5.53 µg/dL show inverse associations between PbB and pulmonary functions tests, including FEV₁ and FVC (Little et al. 2017). Increased bronchial reactivity in response to methacholine challenge, consistent with a diagnosis of asthma, was observed in adults with mean PbB of 2.96 µg/dL (Min et al. 2008a). In addition, risk of obstructive lung disease was observed in a large NHANES population of adults with a mean PbB of 1.73 µg/dL (Rokadia and Agarwal 2013). Studies in children examining associations between PbB and risk of asthma do not provide consistent results. A large prospective study showed an increased risk of asthma in black children with PbB <5 and ≥5 µg/dL compared to white children with PbB <5 µg/dL; however, no increased risk was observed for white children with PbB ≥5 µg/dL compared to white children with PbB <5 µg/dL (Joseph et al. 2005). The underlying causes for the racial disparity of results have not been established. However, the study authors noted the following as possible contributors: socio-economic factors; racial differences in IgE; differences in housing conditions and indoor Pb sources (e.g., Pb paint); and genetic variability in susceptibility to Pb toxicity (e.g., vitamin D receptor gene). In cross-sectional studies, asthma risk was

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Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^b
Decreased lung function			
Chung et al. 2015	Mean: 2.50	FVC%	Correlation coefficient: 0.070
	Tertiles:	FEV ₁ %	Correlation coefficient: 0.00
	• T1: <2.03		
	• T2: 2.03–2.81	FEV ₁ /FVC ratio	Correlation coefficient: -0.115; $p < 0.01^*$
	• T3: >2.81		OR T3: 0.006 (0, 0.286)*
			p-trend: 0.03*
Leem et al. 2015	Mean:	FEV ₁ /FVC ratio	Difference (SE) between reference and Q4:
	• Men: 2.92		-0.6 (0.3); $p = 0.025^*$
	• Women: 2.33		
	Quartiles (men and women)		
	• Q1: ≤ 1.85 (reference)		
	• Q2: 1.86–2.43		
	• Q3: 2.44–3.16		
	• Q4: ≥ 3.17		
Little et al. 2017	Mean:	FVC	Boys, β (SE), per log10 increase in PbB:
	• Boys: 5.27		-5.11 (4.47); $p = 0.25$
	• Girls: 3.82		Girls, β (SE), per log10 increase in PbB:
			-12.90 (5.25); $p = 0.02^*$
Zeng et al. 2017	PbB:	FEV ₁	Regression coefficient for exposed: -
	Median		0.02 (-0.100, 0.043)
	• Control: 3.57	FVC	Regression coefficient for exposed:
	• Exposed: 5.53		FVC: -0.015 (-0.093, 0.063)
Increased bronchial responsiveness			
Min et al. 2008a	Mean (SD): 2.96 (1.59)	BR	A 1 $\mu\text{g}/\text{dL}$ increase in PbB was associated with a higher BR; β (SE): 0.018 (0.007)*
Cross-sectional study; n=523 adults			

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Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Asthma			
Joseph et al. 2005	Mean	Asthma	All compared to PbB <5 µg/dL in white children
Prospective study; n=4,634 children (ages 3 months to 3 years)	<ul style="list-style-type: none">White: 3.2Black: 5.5		HR white (PbB ≥5): 2.3 (0.8, 6.7); p=0.12
			HR black (PbB <5): 1.8 (1.3, 2.4); p<0.01*
			HR black (PbB ≥5): 1.5 (1.2, 1.8); p<0.01*
			HR black (PbB ≥10): 3.0 (1.2, 7.1); p=0.01*
Rokadia and Agarwal 2013^c	Mean	OLD	OR for all OLD: 1.94 (1.10, 3.42)*
Pooled cross-sectional study; n=9,575 adults (8,411 without OLD; 1,164 with OLD)	<ul style="list-style-type: none">Non-OLD: 1.18OLD: 1.73		OR for mild OLD: 1.21 (0.55, 2.65)
			OR for moderate-severe OLD: 3.49 (1.70, 7.15)*
Wang et al. 2017a	Gmean (GSD)	Asthma	OR (all participants), <5 versus ≥5 µg/dL: 5.50 (1.69, 17.94); p=0.005*
Cross-sectional study; n=930 children (mean age: 5.74 years)	<ul style="list-style-type: none">All: 1.86 (1.21)Boys: 1.89 (1.22)Girls: 1.83 (1.20)		OR (boys), <5 versus ≥5 µg/dL: 6.40 (1.49, 27.42); p=0.012*
			OR (girls), <5 versus ≥5 µg/dL: 4.73 (0.44, 50.60); p=0.199
Wells et al. 2014^c	Gmean: 1.07	Asthma	OR for asthma with atopy: 0.97 (0.61, 1.55)
Cross-sectional study; NHANES 2005–2006; n=1,430 children (ages 4–12 years)			OR for asthma with no atopy: 1.07 (0.86, 1.33)

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Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Zeng et al. 2016	Median	Asthma	OR for asthma at PbB ≥5 µg/dL: 9.50 (1.16, 77.49); p<0.01*
Cross-sectional study; n=470 children (ages 3–8 years)	<ul style="list-style-type: none">Haojiang area: 4.75Guiyu area: 6.24		

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 2 for more detailed descriptions of studies.

^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

^cStudy population was from NHANES.

BR = bronchial responsiveness; CI = confidence interval; FEV₁ = forced expiratory volume in 1 second (L/s); FEV₁% = percent of predicted FEV₁; FVC = forced vital capacity (L); FVC% = percent of predicted FVC; Gmean = geometric mean; GSD = geometric standard deviation; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

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increased in Taiwanese children, with elevated risks in the total population and for boys, but not for girls (Wang et al. 2017a) and in Chinese children with PbB ≥ 5 $\mu\text{g/dL}$ (Zeng et al. 2016). In contrast, a large cross-sectional study of children participating in NHANES did not observe an association between PbB (mean 1.07 $\mu\text{g/dL}$) and asthma, with or without atopy (Wells et al. 2014).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to the respiratory system. EPA (2014c) specifically noted that oxidative stress through reactive oxygen species (ROS), resulting in tissue damage and inflammation and immune effects, is a plausible mechanism for the underlying cause of respiratory damage. Increased ROS, along with depletion of antioxidants, results in inflammation and production and release of metabolites and cytokines. Immune-mediated inflammation is observed with asthma and bronchial hyperreactivity.

2.6 CARDIOVASCULAR

Overview. A large number of epidemiological studies showing adverse effects on the cardiovascular system associated with Pb exposure have been published. Most studies evaluated effects in adults, although a few studies in children have been conducted. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome, with results providing consistent evidence of positive associations between Pb exposure and blood pressure. Other cardiovascular endpoints (atherosclerosis, cardiac conduction, cardiovascular disease, and mortality due to cardiovascular disease) also show positive and inverse associations with PbB, although the majority of studies had positive associations. In some cases, although no associations between PbB and cardiovascular outcomes were observed, associations were observed for bone Pb, a biomarker of cumulative Pb exposure that, among individuals with high historical Pb exposures, typically remains elevated for many years after the PbB declines to ≤ 10 $\mu\text{g/dL}$; these cases are noted in the discussions below.

The following cardiovascular effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Greater systolic and diastolic blood pressure:
 - In adults; corroborated in multiple studies.
 - In children; evaluated in a few studies.
 - During pregnancy; evaluated in a few studies.

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- Greater risk of hypertension:
 - In adults, including during pregnancy; evaluated in numerous studies.
- Greater risk of atherosclerosis; evaluated in a few studies.
- Altered cardiac conduction; evaluated in a few studies.
- Greater risk of mortality due to cardiovascular diseases; evaluated in a few studies with mixed results.
- >10 µg/dL:
 - Increased systolic and diastolic blood pressure:
 - In adults; corroborated in multiple studies and meta-analyses.
 - In children; evaluated in a few studies.
 - Increased risk of hypertension; corroborated in multiple studies.
 - Atherosclerosis; evaluated in a few studies.
 - Increased risk or prevalence of heart disease; evaluated in a few studies.
 - Increased mortality due to cardiovascular diseases; corroborated in multiple studies.

Measures of Exposure. PbB and bone Pb concentrations have been used as biomarkers to evaluate cardiovascular effects of Pb exposure. However, PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of Pb. Because the development of cardiovascular effects has a long latency period, associations between PbB and cardiovascular disease at concurrent PbB ≤10 µg/dL may be related to higher past Pb exposures. Bone Pb, a metric of cumulative or long-term exposure to Pb, appears to be a better predictor of Pb-induced elevations in blood pressure and alterations in cardiac conduction than PbB.

Confounding Factors and Effect Modifiers. Numerous factors affect blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, LDL cholesterol levels, and various dietary factors (e.g., dietary calcium). In addition, renal disease, as well as Pb-induced renal damage, can lead to cardiovascular effects, including increased blood pressure (EPA 2014c; NTP 2012); thus, interpretation of studies examining cardiovascular outcomes is complicated by the link between cardiovascular and renal function. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome (e.g., Møller and Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between PbB and blood pressure, if alcohol consumption contributes to Pb intake and, thereby, PbB (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Varying approaches and breadth of

inclusion of these may account for the disparity of results that have been reported. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000). Ambulatory measurements also can decrease bias in estimates related to increases in blood pressure that can accompany clinic visits (Yang et al. 2018).

Characterization of Effects. General trends between studies showing a relationship between PbB and cardiovascular effects are shown in Table 2-6. Over the PbB range of ≤ 10 – >50 $\mu\text{g/dL}$, results of epidemiological studies provide evidence for increased blood pressure and hypertension, atherosclerosis (increased intimal medial thickening and peripheral artery disease), heart disease (myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina), and increased risk of mortality due to cardiovascular diseases. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome. A review by Navas-Acien et al. (2007) concluded that available literature provides evidence that “is sufficient to infer a causal relationship of Pb exposure and hypertension” and evidence that “is suggestive but not sufficient to infer a causal relationship of Pb exposure with clinical cardiovascular outcomes” (cardiovascular, coronary heart disease, and stroke mortality; and peripheral arterial disease). Well-controlled studies in laboratory animals provide additional support regarding effects of Pb on blood pressure; see EPA (2014c) for additional information.

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) ($\mu\text{g/dL}$)	Effects associated with Pb exposure	References
≤ 10	Increased blood pressure and hypertension	Almeida Lopes et al. 2017; Al-Saleh et al. 2005; Barry et al. 2019; Bost et al. 1999; Bushnik et al. 2014; Cheng et al. 2001; Chu et al. 1999; Den Hond et al. 2002; Disha et al. 2019; Elmarsafawy et al. 2006; Faramawi et al. 2015; Gambelunghe et al. 2016; Gerr et al. 2002; Glenn et al. 2003; Gump et al. 2005, 2011; Hense et al. 1993; Hu et al. 1996a; Korrick et al. 1999; Lee et al. 2016a, 2016b; Martin et al. 2006; Muntner et al. 2005; Nash et al. 2003; Obeng-Gyasi and Obeng-Gyasi 2018; Park et al. 2009b; Perlstein et al. 2007; Proctor et al. 1996; Rothenberg et al. 2002; Schwartz 1995; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003; Wells et al. 2011; Yang et al. 2017, 2018; Yazbeck et al. 2009; Zhang et al. 2011; Zota et al. 2013

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Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Atherosclerosis ^a	Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004;
	Heart disease ^b and cardiac function	Chen et al. 2017; Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Jing et al. 2019; Park et al. 2009a
	Mortality due to cardiovascular disease	Aoki et al. 2016; Khalil et al. 2009; Lanphear et al. 2018; Menke et al. 2006; Schober et al. 2006; Weisskopf et al. 2009
>10–30	Increased blood pressure and hypertension	Coate and Fowles 1989; Factor-Litvak et al. 1999; Grandjean et al. 1989; Han et al. 2018; Harlan et al. 1985; Møller and Kristensen 1992; Pirkle et al. 1985; Rabinowitz et al. 1987
	Atherosclerosis ^a	Pocock et al. 1988; Poreba et al. 2011, 2012
	Heart disease ^b and cardiac function	Karakulak et al. 2019; Poreba et al. 2013
	Mortality due to cardiovascular disease	Barry and Steenland 2019; Lustberg and Silbergeld 2002; Min et al. 2017; Schober et al. 2006; Steenland et al. 2017
>30–50	Increased blood pressure and hypertension	Aiba et al. 1999; Al-Saleh et al. 2005; Factor-Litvak et al. 1996, 1999; Ghiasvand et al. 2013; Glenn et al. 2006; Rapisarda et al. 2016; Weaver et al. 2008; Weiss et al. 1986, 1988
	Atherosclerosis ^a	Karakulak et al. 2017
	Heart disease ^b	Bockelmann et al. 2002; Jain et al. 2007; Kieltucki et al. 2017
	Mortality due to cardiovascular disease	Barry and Steenland 2019; Gerhardsson et al. 1995a; Steenland et al. 2017
>50	Increased blood pressure and hypertension	Kirby and Gyntelberg 1985; Were et al. 2014
	Atherosclerosis ^a	Kirby and Gyntelberg 1985
	Mortality due to cardiovascular disease	Cooper 1988; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1995a; McDonald and Potter 1996

^aAtherosclerosis includes increased intimal medial thickening and peripheral artery disease.^bHeart disease includes myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina.

Numerous studies provide a weight of evidence for associations between PbB and increased blood pressure over a wide PbB range in adults (Table 2-6). Results of meta-analyses estimate small but consistent increases in blood pressure per doubling of PbB. The largest meta-analysis of 31 studies published between 1980 and 2001 included a total of 58,518 subjects (Nawrot et al. 2002); blood pressure

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data from studies included in the analysis are shown in Table 2-7 and Figures 2-2 and 2-3. Nawrot et al. (2002), in an update of an earlier meta-analysis by Staessen et al. (1994), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI 0.5, 1.4) and the increase in diastolic pressure to be 0.6 mmHg (95% CI 0.4, 0.8). The range of mean (or median) PbBs for studies included in the analysis was 2.28–63.82 µg/dL. Although a PbB mean was not estimated for the entire study population, only nine studies had a mean PbB <10 µg/dL; therefore, it is likely that the overall PbB mean for the entire study population was >10 µg/dL. Similar outcomes were observed in two other meta-analyses (Schwartz 1995; Staessen et al. 1994). A meta-analysis reported by Staessen et al. (1994) included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI 0.4, 1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI 0.2, 1.0) increase in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI 0.87, 1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error (SE) on effect measurement (e.g., increase in blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis. The estimated increase in blood pressure per doubling of PbB in these meta-analyses is small; however, on a population basis, the consequences of increased blood pressure includes increased risks of serious and potentially fatal effects, including atherosclerosis, stroke, and myocardial infarction. Increased blood pressure during pregnancy has been associated with PbB and bone Pb (Rothenberg et al. 2002; Wells et al. 2011; Yazbeck et al. 2009); these studies are discussed in more detail below (*Effect at Blood Pb Levels ≤10 µg/dL*).

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number ^a	Population ^b	Men (%) ^c	HT ^d	Age (years) ^e	SBP ^f	DBP ^f	Lead (µg/dL) ^g
1 ^h	Pocock et al. 1984 ^{ij} ; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3) ^{a,e}
2	Kromhout 1988 ^{ij} ; Kromhout et al. 1985 ⁱ	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97) ^{a,c}
3	Moreau et al. 1982 ^j , 1988; Orssaud et al. 1985 ^{ij}	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94) ^{a,e}
4	Weiss et al. 1986 ⁱ , 1988 ⁱ	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01) ^{m,x}

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Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number ^a	Population ^b	Men (%) ^c	HT ^d	Age (years) ^e	SBP ^f	DBP ^f	Lead (µg/dL) ^g
5	de Kort and Zwennis 1988 ^{ij} ; de Kort et al. 1987 ⁱ	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29) ^{a,e}
6	Lockett and Arbuckle 1987 ⁱ	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52) ^{a,e}
7	Parkinson et al. 1987 ⁱ	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52) ^{a,c}
8	Rabinowitz et al. 1987 ⁱ	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15) ^{a,c}
9	Elwood et al. 1988a ^{ij} , 1988b ^k	1,136	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11) ^{g,c}
10	Elwood et al. 1988a, 1988b ^{ij,l}	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21) ^{g,c}
11	Gartside et al. 1988 ⁱ ; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992 ^m	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93) ^{g,e}
12	Neri et al. 1988 ^{ij,n}	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06) ^{a,e}
13	Neri et al. 1988 ^{i,o}	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03) ^{m,e}
14	Grandjean et al. 1989, 1991 ^{i,p}	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09) ^{a,e}
15	Reimer and Tittelbach 1989 ⁱ	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24) ^{a,c}
16	Apostoli et al. 1990 ⁱ	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18) ^{a,e}
17	Morris et al. 1990 ^{ij}	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95) ^{a,e}
18	Sharp et al. 1988 ^{ij} , 1989 ⁱ , 1990 ⁱ	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92) ^{p,e}
19	Staessen et al. 1984 ^{i,q}	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22) ^{g,e}
20	Møller and Kristensen 1992 ^{ij,r}	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09) ^{a,e}
21	Hense et al. 1993 ^{ij}	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09) ^{a,e}
22	Maheswaran et al. 1993 ⁱ	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01) ^{a,e}
23	Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)

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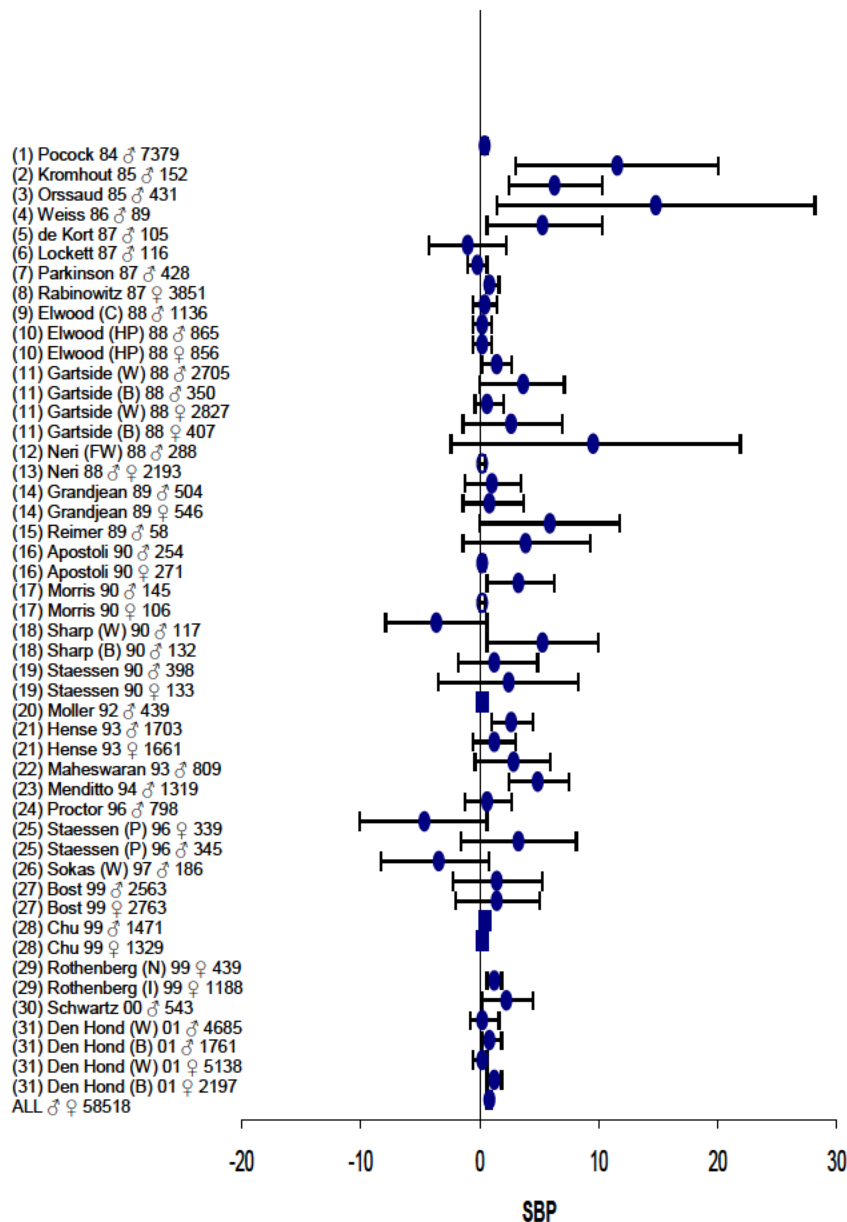
Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

Reference	Number ^a	Population ^b	Men (%) ^c	HT ^d	Age (years) ^e	SBP ^f	DBP ^f	Lead (µg/dL) ^g
24 Hu et al. 1996a; Proctor et al. 1996 ^s	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02) ^{p,e}
25 Staessen et al. 1996a ⁱ , 1996b ^{i,t}	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52) ^{g,e}
26 Sokas et al. 1997 ^u	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04) ^{p,e}
27 Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?) ^g
28 Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69) ^{a,e}
29 Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?) ^g
30 Schwartz et al. 2000c	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1) ^{a,e}
31 Den Hond et al. 2001 ^v	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94) ^{g,e}

^aNumber of persons in whom relevant data were available.^bStudy population: BC = blue collar workers; GP = sample from general population; WC = white collar employees.^cMen: Percentage of men.^dHT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.^eAge: Mean age or midpoint of age span (range or approximate range given between parentheses).^fSBP, DBP: Mean systolic and diastolic blood pressures.^gLead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P₅₀ (median). The spread of blood lead is given between parentheses: c = P₅–P₀₅ interval; P₁₀–P₉₀ interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.^hNumber refers to reference in Figures 2-2 and 2-3.ⁱIncluded in the Staessen et al. (1994) meta-analysis.^jIncluded in the Schwartz (1995) meta-analysis.^kCaerphilly Study.^lWelsh Heart Program.^mNHANES (National Health and Nutrition Examination Survey).ⁿFoundry workers.^oCanadian Health Survey.^pGlostrup Population Study, cross-sectional analysis (1976).^qLondon Civil Servants.^rGlostrup Population Study, longitudinal analysis (1976–1987).^sNormative Aging Study.^tPheeCad (Public Health and Environmental Exposure to Cadmium) Study.^uBecause of missing information, only the effect in whites is included.^vNHANES III.

Source: Nawrot et al. 2002

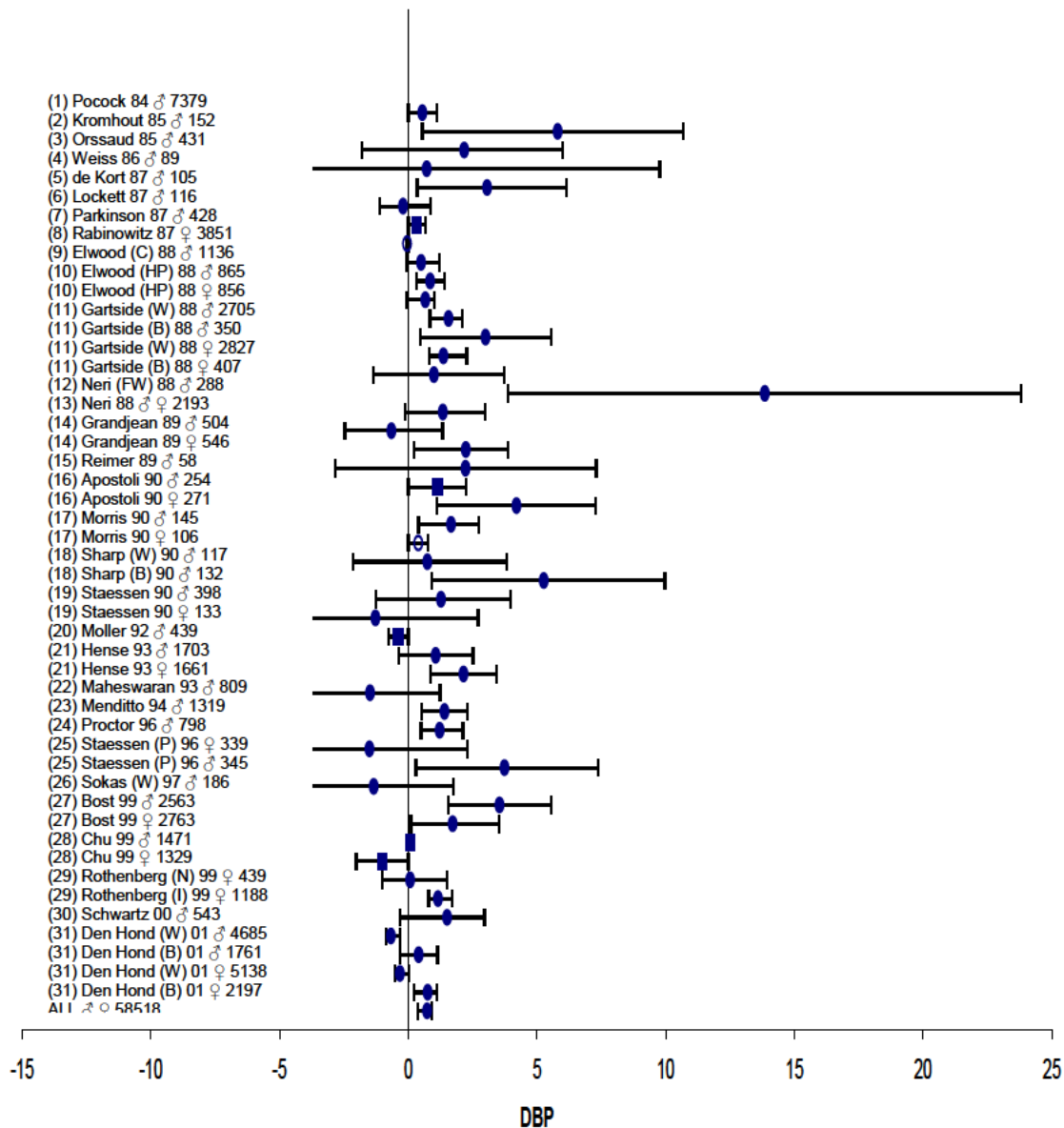
2. HEALTH EFFECTS

Figure 2-2. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*

*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

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Figure 2-3. Change in the Diastolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*

*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; N = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

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Within individual studies, dose-effect relationships are evident at PbB ≤ 10 $\mu\text{g/dL}$. A positive dose-effect was observed for PbB and diastolic blood pressure (Zota et al. 2013). An observed positive dose-effect was observed for tibia Pb concentration and hypertension (Hu et al. 1996a). No dose-effect was observed for PbB and pulse pressure (PP), although a positive dose-effect was observed for tibia Pb and PP (Perlstein et al. 2007). In a cross-sectional study of women, diastolic hypertension was observed to have a positive dose-effect when pre- and postmenopausal women were analyzed together and when postmenopausal women were analyzed alone. In contrast, a dose-effect relationship was not observed for PbB and hypertension in a cross-sectional study of men and women (Muntner et al. 2005). A positive dose-effect relationship was observed for PbB and peripheral artery disease (PAD) (Muntner et al. 2005). In men, tibia blood levels had a positive dose-effect relationship with QT interval, but a negative dose-effect relationship with atrioventricular conduction defect (Eum et al. 2011). Studies have also found positive dose-effect relationships between mortality due to cardiovascular disease, myocardial infarction, and stroke and PbB (Menke et al. 2006; Schober et al. 2006).

Several studies have evaluated associations between PbB and cardiovascular function in children (Ahn et al. 2018; Factor-Litvak et al. 1999, 1996; Gump et al. 2005, 2011; Kapuku et al. 2006; Khalil et al. 2009, 2010; Lustberg and Silbergeld 2002; Menke et al. 2006; Schober et al. 2006; Zhang et al. 2011). Results show alterations in cardiovascular function, including increases in blood pressure and altered cardiovascular function under stress (decreased stroke volume and cardiac output) over a PbB range from <10 to approximately 40 $\mu\text{g/dL}$.

Effect at Blood Pb Levels ≤ 10 $\mu\text{g/dL}$. Studies investigating relationships between PbB ≤ 10 $\mu\text{g/dL}$ and cardiovascular effects have evaluated effects on blood pressure (including hypertension), atherosclerosis, heart disease (alterations in cardiac conduction and ischemic heart disease), and death due to cardiovascular disease.

Increased blood pressure and hypertension. Numerous studies of large populations show associations between PbB ≤ 10 $\mu\text{g/dL}$ and increased systolic and/or diastolic blood pressure and increased risk of hypertension and prehypertension (see Table 2-8). The lowest mean PbB associated with increased systolic and diastolic is 1.33 $\mu\text{g/dL}$ (Obeng-Gyasi and Obeng-Gyasi 2018). A few studies did not show associations between PbB and blood pressure parameters; however, positive associations between bone Pb concentrations and blood pressure at concomitant PbB ≤ 10 $\mu\text{g/dL}$ were observed (Barry et al. 2019; Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Zhang et al. 2011). Studies are briefly summarized

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Women and men combined (not stratified by sex)^c			
Almeida Lopes et al. 2017	Gmean: 1.97 Quartiles:	SBP	Change in SBP, Q4: -0.00 (-0.00, -0.00); p-trend: 0.002*
Population-based study; n=948 adults (≥40 years of age)	• Q1: ≤1.32 • Q2: 1.32–1.93 • Q3: 1.93–2.76 • Q4: >2.76	DBP	Change in DBP, Q4: 0.06 (0.04, 0.09); p-trend: <0.001*
		Hypertension	OR, Q4: 2.54 (1.17, 5.53)*
Faramawi et al. 2015^d	Mean: 3.44	SBP	β (SE), mmHg for change in blood pressure SD per µg/dL: 0.07 (0.02); p<0.01*
Cross-sectional study; n=13,757		DBP	β (SE), for change in blood pressure SD per µg/dL: 0.04 (0.03); p=0.08
Gambelunghe et al. 2016	Mean: 2.8 Quartiles:	SBP	Regression coefficient, β, Q4 versus Q1–Q3 (mmHg): 1.7; p=0.01*
Cross-section study; n=4,452 adults	• Q1: 0.15–1.9 • Q2: 1.9–2.5 • Q3: 2.5–3.3 • Q4: 3.3–25.8	DBP	Regression coefficient, β, Q4 versus Q1–Q3 (mmHg): 1.3; p<0.001*
		Hypertension	OR, Q4 versus Q1–Q3: 1.3 (1.1–1.5); p=0.004*
Lee et al. 2016^b	Study population mean not reported Quartiles:	Prehypertension	OR, versus Q1: • Q2: 1.24 (1.04, 1.48)* • Q3: 1.27 (1.06, 1.52)* • Q4: 1.30 (1.07, 1.60)* • p-trend: 0.0152*
Cross-sectional study; n=8,493 adults	• Q1: 0.206–1.539 • Q2: 1.540–2.056 • Q3: 2.057–2.716 • Q4: 2.717–24.532		
Martin et al. 2006	Mean: 3.5	SBP	β, mmHg per 1 µg/dL: 0.99 (0.47, 1.51); p<0.01*
Cross-sectional study; n=964 (ages 50– 70 years)		DBP	β, mmHg per 1 µg/dL: 0.51 (0.24, 0.79); p<0.01*

2. HEALTH EFFECTS

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Zota et al. 2013^d	Mean: 1.69 Quintiles:	Elevated SBP (≥140 mmHg)	OR (Q5): 1.23 (0.92, 1.65); p-trend: 0.06
Cross-sectional study; n=8,194 (ages 40–65 years)	<ul style="list-style-type: none"> • Q1: ≤1.05 • Q2: 1.06–1.44 • Q3: 1.45–1.90 • Q4: 1.91–2.69 • Q5: >2.70 	Elevated DBP (≥90 mmHg)	OR (Q3): 1.56 (1.11, 2.19)* OR (Q4): 1.80 (1.24, 2.60)* OR (Q5): 1.77 (1.25, 2.50)* p-trend 0.0002
Obeng-Gyasi and Obeng-Gyasi 2018	Mean: 1.33	SBP	β, increase in blood pressure (mmHg) per unit increased in ln PbB: 0.238 (0.122, 0.355); p=0.0001*
Cross-sectional study; n=22,747 adults		DBP	β, increase in blood pressure (mmHg) per unit increased in ln PbB: 0.132 (0.049, 0.215); p=0.002*
Women and men (stratified by sex)^c			
Bost et al. 1999	Mean	SBP	M: no association with PbB (regression coefficient not reported)
Cross-sectional study; n=2,563 males and 2,763 females	<ul style="list-style-type: none"> • M: 3.7 • F: 2.6 		F: no association with PbB (regression coefficient not reported)
		DBP	M: β, per doubling of PbB: 0.78 (0.01, 1.55)* F: regression coefficients not reported
Bushnik et al. 2014	Mean	SBP	All β, mmHg per 1 µg/dL: 1.85 (-0.20, 3.90); p=0.075
Population-based survey; n=2,214 males and 2,336 females	<ul style="list-style-type: none"> • All: 1.64 • Non-hypertensive: 1.59 • Hypertensive: 1.74 		M β, mmHg per 1 µg/dL: 2.17 (-0.08, 4.42); p=0.058 F β, mmHg per 1 µg/dL: 0.76 (-2.72, 4.24); p=0.656
		DBP	All β, mmHg per 1 µg/dL: 1.91 (0.75, 3.08); p=0.002* M β, mmHg per 1 µg/dL: 2.36 (0.94, 3.79); p=0.002*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
			F β, mmHg per 1 µg/dL: 1.43 (-0.51, 3.38); p=0.142
		Hypertension	All β, mmHg per 1 µg/dL: -3.87 (-7.46, -0.29); p=0.035*
			M β, mmHg per 1 µg/dL: -6.37 (-15.02, 2.29); p=0.142
			F β, mmHg per 1 µg/dL: -4.18 (-8.78, 0.42); p=0.073
Chu et al. 1999	Mean	SBP	M β (SE), mmHg per 1 log₁₀ µg/dL: 0.185 (0.076); p=0.015*
Population-based survey study; n=1,471 males and 1,329 females	<ul style="list-style-type: none"> • M: 7.3 • F: 5.7 		F β (SE), mmHg per 1 log ₁₀ µg/dL: -0.057 (0.109); p=0.603
		DBP	M β (SE), mmHg per 1 log ₁₀ µg/dL: 0.075 (0.053); p=0.159
			F β (SE), mmHg per 1 log ₁₀ µg/dL: -0.083 (0.072); p=0.250
Hense et al. 1993	Mean	SBP	M β, mmHg per 1 µg/dL: 0.29 (0.08, 0.49)*
Population-based survey study; n=1,703 males and 1,661 females	<ul style="list-style-type: none"> • M: 8.3 • F: 6.0 		F β, mmHg per 1 µg/dL: 0.17 (-0.14, 0.48)
		DBP	M β, mmHg per 1 µg/dL: 0.08 (-0.06, 0.23)
			F β, mmHg per 1 µg/dL: 0.29 (0.09, 0.49)*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Lee et al. 2016a	Gmean (95% CI)	SBP	M difference, T3 versus T1: 0.25 (-0.90, 1.41)
Cross-sectional study; n=5,920 men and 6,059 women	<ul style="list-style-type: none"> Men: 2.396 Women: 1.919 Tertiles: <ul style="list-style-type: none"> Men <ul style="list-style-type: none"> T1: <2.096 T2: 2.096–2.886 T3: >2.886 Women <ul style="list-style-type: none"> T1: <1.516 T2: 1.516–2.147 T3: >2.14 	DBP	F difference, T3 versus T1: 1.48 (0.29, 2.67)
			M difference, T3 versus T1: 0.73 (-0.12, 1.60)
			F difference, T3 versus T1: 1.059 (0.308, 1.811)
		Hypertension	M OR, T3: 0.88 (0.72, 1.07)
		Prehypertension	F OR, T3: 1.26 (0.999, 1.58)
			M OR, T3: 0.95 (0.79, 1.16)
			F OR, T3: 1.22 (1.01, 1.48)*
Men only^c			
An et al. 2017	Gmean: 5.839	SBP	β, per doubling of PbB: -0.636 (-2.661, 1.389); p=0.537
Cross-sectional study; n=310 male smelters (21–61 years of age)		DBP	β, per doubling of PbB: -1.182 (-2.763, 0.399); p=0.142
Barry et al. 2019	Median (range): 2.5 (0–34.0)	SBP	Regression coefficient (SE) for PbB Q4: 7.33 (4.40); p=0.10
Cross-sectional study; n=211 male Pb workers	<ul style="list-style-type: none"> Quartiles <ul style="list-style-type: none"> Q1: <1.6 Q2: 1.6–2.5 Q3: 2.6–4.2 Q4: ≥4.3 		PbB continuous: 0.19 (0.30) 0.52
			Bone Pb Q4: 5.32 (5.26); p=0.31
			Bone Pb continuous: 0.36 (0.15); p=0.02*
	Bone Pb (tibia) median, µg/g (range): 13.8 (0–127.3)		
	<ul style="list-style-type: none"> Bone Pb quartiles: <ul style="list-style-type: none"> Q1: <9.6 Q2: 9.6–13.7 Q3: 13.8–19.5 Q4: ≥19.6 		

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Cheng et al. 2001^e	PbB mean (all): 6.09	Hypertension (borderline and definite)	RR, per 1 SD increase in PbB: 1.00 (0.76, 1.33)
Longitudinal study; n=833 men	Tibia Pb (µg/g)		RR, per 1 SD increase in tibia Pb: 1.22 (0.95, 1.57)
Analysis for hypertension limited to 474 participants who had no history of definite hypertension; analysis for SBP limited to 519 participants who were free from definite hypertension at baseline	<ul style="list-style-type: none"> • Borderline: 23.46 • Definite: 22.69 Patella Pb (µg/g) <ul style="list-style-type: none"> • Borderline: 33.73 • Definite: 32.72 	SBP	RR, per 1 SD increase in patella Pb: 1.29 (1.04, 1.61); p<0.05*
			RR, per 1 SD increase in PbB: -0.13 (-1.35, 1.09)
			RR, per 1 SD increase in tibia Pb: 1.37 (0.02, 2.73); p<0.05*
			RR, per 1 SD increased in patella Pb: 0.57 (-0.71, 1.84)
Elmarsafawy et al. 2006^e	Mean	Hypertension	Low Ca ²⁺ : OR: 1.07 (1.00, 1.15)*
Cross-sectional study; n=471	<ul style="list-style-type: none"> • Low Ca²⁺ intake: 6.6 • High Ca²⁺ intake: 6.6 		High Ca ²⁺ : OR: 1.03 (0.97, 1.11)
Glenn et al. 2003	Mean: 4.6	SBP	β (SE; 95% CI), per 1 SD increased in PbB: 0.64 (0.25; 0.14, 1.14)*
Occupational longitudinal study; n=496		DBP	β (SE; 95% CI); per 1 SD increased in PbB: 0.09 (0.17; -0.24, 0.43)
Hu et al. 1996a^e	Mean	Hypertension	Risk of hypertension based on tibia Pb: logistic β (SE): 0.19 (0.0078); p=0.01*
Case-control study of men (n=146) with hypertension and controls (n=444)	<ul style="list-style-type: none"> • Cases: 6.9 • Controls: 6.1 		PbB was not associated with hypertension
			OR for 1 µg/g change in tibia Pb: 1.019 (1.004, 1.035)*
			OR for quintile range (8–37 µg/g): 1.5 (1.1, 1.8)*
Perlstein et al. 2007^e	Mean: 6.12	PP	PbB: no trend over quintiles (p=0.82)
Cross-sectional study; n=593			Bone Pb: p-trend=0.02*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Proctor et al. 1996^e			
	Mean:	SBP	All β, mmHg per 1 In µg/dL PbB: 0.85 (-1.1, 2.7); p>0.05
Cross-sectional study; ≤74 years (n=681); >74 years (n=117)	<ul style="list-style-type: none"> All: 6.5 ≤74 years: 6.5 >74 years: 6.3 		<ul style="list-style-type: none"> ≤74 β, mmHg per 1 In µg/dL PbB: 1.2 (-0.86, 3.2); p>0.05
		DBP	All β, mmHg per 1 In µg/dL PbB: 1.2 (0.11, 2.2); p≤0.05*
			≤74 β, mmHg per 1 In µg/dL PbB: 1.6 (0.42, 2.7); p≤0.01*
Yang et al. 2018			
Cross-sectional study; n=236 Pb workers	Gmean (IQR): 4.50 (2.60–9.15)	SBP	Regression (β) coefficients, expressed as change pressure (mmHg) per 2-fold increase in PbB: <ul style="list-style-type: none"> Office blood pressure: 0.79 (-0.17, 1.76) p=0.11 24-hour ambulatory pressure: 0.29 (-0.82, 1.41) p=0.60
		DBP	Regression (β) coefficients, expressed as change pressure (mmHg) per 2-fold increase in PbB: <ul style="list-style-type: none"> Office: 0.87 (0.03, 1.72) p=0.043* 24-hour ambulatory: -0.25 (-0.97, 0.48) p=0.50
		Hypertension	OR: <ul style="list-style-type: none"> Office: 0.89 (0.62–1.28); p=0.052 24-hour ambulatory: 1.21 (0.94–1.57); p=0.14
Women only^c			
Al-Saleh et al. 2005	Mean	Hypertension	OR for PbB ≥3.85 compared to PbB <3.85: 5.27 (0.93, 29.86); p=0.06
Case-control study of women with hypertension (n=100) and control subjects (n=85)	<ul style="list-style-type: none"> Hypertension: 4.75 Controls: 4.56 		

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Korrick et al. 1999 Case-control study of women with hypertension (n=89) and control subjects (n=195)	Mean (all): 3	Hypertension	PbB: no increased risk (ORs not reported) Patella Pb OR per 1 µg/g increase in PbB: 1.03 (1.00, 1.05); p=0.02*
Nash et al. 2003 Cross-sectional study; n=2,165 all; 1,084 premenopausal, and 663 postmenopausal	Mean (all): 2.9 Quartiles; mean (range) • Q1: 1.0 (0.5–1.6) • Q2: 2.1 (1.7–2.5) • Q3: 3.2 (2.6–3.9) • Q4: 6.4 (4.0–31.1)	SBP	All β (SE), mmHg per 1 In µg/dL PbB: 0.32 (0.16); p=0.03* Premenopausal β (SE), mmHg per 1 In µg/dL PbB: 0.14 (0.26); p=0.59 Postmenopausal β (SE), mmHg per 1 In µg/dL PbB: 0.42 (0.21); p=0.29
		DBP	All β (SE): 0.25 (0.09), mmHg per 1 In µg/dL PbB; p=0.009* Premenopausal β (SE), mmHg per 1 In µg/dL PbB: 0.38 (0.25); p=0.12
			Postmenopausal β (SE) mmHg per 1 In µg/dL PbB: 0.14 (0.13); p=0.04*
		Hypertension	Percent of total population with hypertension: p-trend<0.001* (Q1: 19.4; Q2: 20.6; Q3: 25.5 Q4: 28.3)
Women and men stratified by race^c			
Den Hond et al. 2002^d Cross-sectional study n=4,685 MW; 5,138 FW; 1,761 MB; and 2,197 FB	Mean • MW: 3.6 • FW: 2.1 • MB: 4.2 • FB: 2.3	SBP	MW β, per doubling of PbB: 0.3 (-0.2, 0.7); p=0.29 FW β, per doubling of PbB: 0.1 (-0.4, 0.5); p=0.80 MB β, per doubling of PbB: 0.9 (0.04,1.8); p=0.04* FB β, per doubling of PbB: 1.2 (0.4,2.0); p=0.004*
		DBP	MW β, per doubling of PbB: -0.6 (-0.9, -0.3); p=0.0003*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Muntner et al. 2005^d			
Cross-sectional study; n=9,961 (men and women), stratified by race (W, B, MA)	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	Hypertension	FW β, per doubling of PbB: -0.2 (-0.5, 0.1); p=0.13 MB β, per doubling of PbB: 0.3 (-0.3, 1.0); p=0.28 FB β, per doubling of PbB: 0.5 (0.01, 1.1); p=0.047*
Park et al. 2009b^d			
Cross-sectional study; n=12,500 all, 2,130 MW (<50 years old); 2,152 MW (≥50 years old); 1,048 MB (<50 years old); 540 MB (≥50 years old); 2,429 FW (<50 years old); 2,180 FW (≥50 years old); 1,409 FB (<50 years old); and 612 FB (≥50 years old)	Mean • MW (<50 years old) 4.02 • MW (≥50 years old) 4.92 • MB (<50 years old) 4.55 • MB (≥50 years old) 7.57 • FW (<50 years old) 2.09 • FW (≥50 years old) 3.53 • FB (<50 years old) 2.52 • FB (≥50 years old) 4.49	Hypertension	MW OR: 1.06 (0.92, 1.22) FW OR: 1.16 (1.04, 1.29)* MB OR: 1.17 (0.98, 1.38) FB OR: 1.19 (1.04, 1.38)* M (<50 years old) OR: 0.98 (0.80, 1.22) M (>50 years old) OR: 1.20 (1.02, 1.41)* F (<50 years old) OR: 1.23 (1.04, 1.46)* F (>50 years old) OR: 1.09 (0.94, 1.26)
Scinicariello et al. 2010^d			
Cross-sectional study; n=6,016 (stratified by race)	Mean • W 2.87 • B 3.59 • MA 3.33	SBP	W β (SE), mmHg per ln µg/dL PbB: 1.05 (0.37); p=0.01* B β (SE), mmHg per ln µg/dL PbB: 2.55 (0.49); p=0.001* MA β (SE), mmHg per ln µg/dL PbB: 0.84 (0.46); p=0.08
		DBP	W β (SE), mmHg per ln µg/dL PbB: -0.14 (0.49); p=0.77

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Scinicariello et al. 2011^d Cross-sectional study; n=16,222 all; 4,538 MW; 4,319 FW; 1,767 MB; 1,854 FB; 1,925 MMA; and 1,819 FMA	Mean <ul style="list-style-type: none">All 1.41MW 2.20FW 1.55MB 2.44FB 1.81MMA 2.47FMA 1.56	SBP	B β (SE), mmHg per ln µg/dL PbB: 1.99 (0.44); p=0.0002* MA β (SE), mmHg per ln µg/dL PbB: 0.74 (0.74); p=0.06
			All β (SE), per ln µg/dL PbB: 1.07 (0.35); p<0.05*
			MW β (SE), per ln µg/dL PbB: 0.87 (0.53); p>0.05
			FW β (SE), per ln µg/dL PbB: 0.89 (0.55); p>0.05
			MB β (SE), per ln µg/dL PbB: 2.30 (0.71); p<0.05*
			FB β (SE), per ln µg/dL PbB: 2.40 (1.14); p<0.05*
			MMA β (SE), per ln µg/dL PbB: 0.10 (0.70); p>0.05
			FMA β (SE), per ln µg/dL PbB: -0.03 (0.64); p>0.05
		DBP	All β (SE): 0.71 (0.27); p<0.05*
			MW β (SE): 0.90 (0.45); p<0.05*
			FW β (SE): 0.95 (0.38); p<0.05*
			MB β (SE): 2.75 (0.82); p<0.05*
			FB β (SE), per ln µg/dL PbB: 0.30 (0.81); p>0.05
			MMA β (SE), per ln µg/dL PbB: -1.34 (0.66); p<0.05*
			FMA β (SE), per ln µg/dL PbB: -0.74 (0.44); p>0.05

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Vupputuri et al. 2003^d	Mean	SBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.29 (-0.24, 0.83)
Cross-sectional study; n=14,952 total; n=5,360 MW; 5,188 FW; 2,104 MB; and 2,300 FB	<ul style="list-style-type: none">• MW 4.4• FW 3.0• MB 5.4• FB 3.4		FW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.34 (-0.49, 1.17)
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.82 (0.19, 1.44); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.55 (0.47, 2.64); p<0.01*
		DBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.01 (-0.38, 0.40); p≥0.05
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: -0.04 (-0.56, 0.47) p≥0.05
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.64 (0.08, 1.20); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.07 (0.37, 1.77); p<0.01*
		Hypertension	MW OR: 1.04 (0.93, 1.16); p=0.47
			FW OR: 1.32 (1.14, 1.52) p<0.001*
			MB OR: 1.08 (0.99, 1.19); p=0.08
			FB OR: 1.39 (1.21, 1.61); p<0.001*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Children and young adults^c			
Ahn et al. 2018			
Cross-sectional study; n=1,776 adolescents (ages 10–18 years)	Mean (95% CI): 1.192 (1.165, 1.219) Quartiles • Males ○ Q1: <1.07 ○ Q2: 1.07–1.341 ○ Q3: 1.342–1.655 ○ Q4: >1.655 • Females ○ Q1: <0.839 ○ Q2: 0.839–1.076 ○ Q3: 1.077–1.371 ○ Q4: >1.371	DBP SBP Prehypertension	Mean difference with doubling of PbB, continuous variable: -0.680 (-1.581, 0.221) Mean difference with doubling of PbB, continuous variable: -0.099 (-1.098, 0.898) OR, continuous variable: 0.906 (0.629, 1.305)
Gerr et al. 2002			
Cross-sectional study; n=508 young adults (ages 19–29 years)	PbB mean associated with the SBP following bone Pb concentrations: • <1 µg/g: 1.91 (1.58) • 1–5 µg/g: 2.31 (2.06) • 6–10 µg/g: 2.43 (2.36) • >10 µg/g: 3.15 (2.28)	SBP DBP	Increase (mmHg) associated with bone Pb >10 µg/g (SE): 4.26 (1.48); p=0.004* Increase (mmHg) associated with bone Pb >10 µg/g (SE): 2.80 (1.25); p=0.03*
Gump et al. 2005			
Prospective study; n=122 children assessed at 9 years of age	Cord PbB mean: 2.97	SBP DBP	β (SE), mmHg log µg/dL: 12.16 (4.96); p=0.016* β (SE), mmHg per log µg/dL: 8.45 (4.54); p=0.066
Gump et al. 2011			
Cross-sectional study; n=140 children (ages 9–11 years)	Mean: 1.01 Quartiles: • Q1: 0.14–0.68 • Q2: 0.69–0.93 • Q3: 0.94–1.20 • Q4: 1.21–3.76	SBP DBP TPR	Under acute stress, p-trend over quartiles: 0.31 Under acute stress, p-trend over quartiles: 0.29 Under acute stress, p-trend over quartiles: 0.03*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Zhang et al. 2011 Prospective longitudinal study; n=457 mother-child pairs; children evaluated at ages 7–15 years	<ul style="list-style-type: none"> • Mean umbilical cord: 5.51 • Mean child concurrent: 2.96 • Median maternal postnatal tibia Pb (µg/g): 9.3 	SBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): -0.34 (-1.98, 1.30) Maternal tibia Pb, girls, β, mmHg increased per maternal tibia Pb (13 µg/g): 2.11 (0.69, 3.52); p=0.025*
		DBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): -0.83 (-2.05, 0.38) Maternal tibia Pb, girls, β, mmHg increased per maternal tibia Pb (13 µg/g): 1.60 (0.28, 2.91); p=0.007*
Blood pressure during pregnancy^c			
Disha et al. 2019 Cross-sectional study; n=44 healthy pregnant women; n=23 pre-eclampsia women	PbB: Mean <ul style="list-style-type: none"> • Control: 2.38 • Pre-eclampsia: 3.42 	SBP	Pearson correlation (mmHg): 0.71; p<0.0001*
		DBP	Pearson correlation (mmHg): 0.57; p=0.004*
Rothenberg et al. 2002 Longitudinal study; n=667 pregnant women	Mean: 1.9	SBP	Ln-PbB, β: -0.04 (-1.26, 1.18)
	Bone (calcaneus) Pb (µg/g) mean: 10.7		Bone Pb, β: 0.70 (0.04, 1.36)*
		DBP	Ln-PbB, β: 0.20 (-0.78, 1.18)
			Bone Pb, β: 0.54 (0.01, 1.08)*
Wells et al. 2011 Cross-sectional study; n=285 pregnant women during labor	Umbilical cord PbB <ul style="list-style-type: none"> • mean: 0.66 • Quartiles: <ul style="list-style-type: none"> ○ Q1: <0.46 ○ Q2: 0.47–0.65 ○ Q3: 0.66–0.95 ○ Q4: 0.96–6.47 	SBP	Q4 versus Q1 increase in SBP in mmHg at admission: 6.87 (1.51, 12.21); p<0.05*
			Q4 versus Q4 maximum increase in SBP in mmHg: 7.72 (1.83, 13.60); p<0.05*
		DBP	Q4 versus Q1 increase in DBP in mmHg at admission: 4.40 (0.21, 8.59); p<0.05*
			Q4 versus Q4 maximum increase in DBP in mmHg: Q4: 8.33 (1.14, 15.53); p<0.05*

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Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^{a,b}
Yazbeck et al. 2009	Mean	PIH	OR for PIH for an increase of 1 log ₁₀ µg/dL in PbB; 3.29 (1.11, 9.74); p=0.03*
Cross-sectional study; n=971 pregnant women	<ul style="list-style-type: none">Participants with PIH: 2.2Participants without PIH: 1.9		

^aAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
^bIf bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
^cSee the *Supporting Document for Epidemiological Studies for Lead*, Table 3 for more detailed descriptions of studies.
^dStudy population was from NHANES.
^eStudy population was from the Normative Aging Study.

B = black; CI = confidence interval; CL = confidence limit; DBP = diastolic blood pressure; F = female(s); Gmean = geometric mean; M = male(s); MA = Mexican American; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PIH = pregnancy-induced hypertension; PP = pulse pressure; RR = rate ratio; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TPR = total peripheral resistance; W = white

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in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3.

The magnitude of effect on blood pressure observed in individual large-scale, cross-sectional studies is consistent with results of meta-analyses (see discussion above on *Characterization of Effects*). For example, Martin et al. (2006) reported that systolic and diastolic blood pressure increased by 0.99 (95% CI 0.47, 1.51; $p < 0.01$) mmHg and 0.51 (95% CI 0.24, 0.79; $p < 0.01$) mmHg, respectively, per 1 $\mu\text{g/dL}$ increase in PbB.

Several studies have examined the relationship between PbB and blood pressure with study populations stratified according to gender, race, and/or age. For example, within study populations, positive associations were observed between PbB and systolic and diastolic blood pressure in men but not in women (Bushnik et al. 2014; Chu et al. 1999; Hense et al. 1993). A cross-sectional study reported an increased risk of prehypertension (defined as a diastolic blood pressure of at least 80 mmHg but below 90 mmHg or a systolic blood pressure of at least 120 mmHg but below 140 mmHg) in women but not in men, although PbB was lower ($p < 0.05$) in women (1.9 $\mu\text{g/dL}$) than men (2.4 $\mu\text{g/dL}$) (Lee et al. 2016a). However, other studies did not find differences between men and women (Bost et al. 1999; Scinicariello et al. 2011). Stratification by sex and age indicates additional differences between men and women. For example, Park et al. (2009b) reported a greater risk of hypertension in men > 50 years of age (odds ratio [OR] 1.20; 95% CI 1.02, 1.41), but not in men < 50 years of age (OR 0.98; 95% CI 0.80, 1.22), whereas in women, the opposite effect of age was observed, with a greater risk of hypertension in women < 50 years of age (OR 1.23; 95% CI 1.04, 1.46) but not > 50 years of age (OR 1.09; 95% CI 0.94, 1.26). Studies that stratify populations by race have found race differences in effect sizes on blood pressure. Large-scale cross-sectional studies based on data from NHANES have found larger effect sizes in non-Hispanic blacks and Mexican-Americans than in whites (Den Hond et al. 2002; Muntner et al. 2005; Scinicariello et al. 2011; Vupputuri et al. 2003). Cross-sectional studies based on data from NHANES have consistently shown elevations of systolic blood pressure in association with increasing PbB among black males and females, with less consistency in findings for other demographic groups or for diastolic blood pressure (Den Hond et al. 2002; Nash et al. 2003; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003). Scinicariello et al. (2011) estimated increases in systolic blood pressure ranging from 1.07 to 2.4 per 1 ln increase in PbB (equivalent to approximately 0.7–1.66 per doubling of PbB). The largest effects sizes were observed in black males (2.3; SE 0.71 per ln PbB) and black females (2.4; SE 1.14). Den Hond et al. (2002) estimated the effect size for systolic blood pressure in black males and females to be 0.9 mmHg (95% CI 0.04, 1.8) and 1.2 mmHg (95% CI 0.4, 2.0) per doubling of PbB, respectively. Vupputuri et al.

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(2003) estimated the effect size for systolic blood pressure in black males and females to be 0.82 mmHg (95% CI 0.19, 1.44) and 1.55 mmHg (95% CI 0.47, 2.64) per 1 standard deviation (SD) increase (3.3 µg/dL) of PbB, respectively. As discussed above (see *Confounding Factors and Effect Modifiers*), numerous co-variables and confounders affect studies of associations between PbB and blood pressure, complicating comparisons between studies.

Few studies have evaluated effects of chronic Pb exposure in children or young adults on blood pressure parameters at PbB at ≤10 µg/dL (Ahn et al. 2018; Gerr et al. 2002; Gump et al. 2005, 2011; Zhang et al. 2011). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Population sizes in these studies are small (n=122–1,776) compared to studies in adults. Positive associations were observed between concurrent PbB and increased systolic and diastolic blood pressure in young adults (Gerr et al. 2002). Two prospective studies suggest that prenatal exposure to Pb is associated with increased blood pressure in childhood (Gump et al. 2005; Zhang et al. 2011). Umbilical cord PbB was positively associated with increased systolic, but not diastolic, blood pressure in children (Gump et al. 2005). Maternal postnatal bone Pb concentration was associated with increased systolic and diastolic blood pressure in girls, but not boys; however, no association was observed between umbilical cord PbB or patella Pb concentration and increased blood pressure (Zhang et al. 2011). No association between PbB and diastolic or systolic blood pressure or risk of prehypertension in a larger population of adolescents (n=1,776) with a mean PbB of 1.19 µg/dL (Ahn et al. 2018).

Effects of Pb on blood pressure and hypertension at PbB at ≤10 µg/dL have also been evaluated during pregnancy (Disha et al. 2019; Rothenberg et al. 2002; Wells et al. 2011; Yazbeck et al. 2009). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Increases in systolic and diastolic blood pressure during pregnancy and labor were associated with PbB ≤10 µg/dL umbilical cord PbB, or bone Pb concentrations with concomitant PbB ≤10 µg/dL (Rothenberg et al. 2002; Wells et al. 2011; Yazbeck et al. 2009). Pregnancy-induced hypertension has been positively associated with PbB ≤10 µg/dL (Yazbeck et al. 2009). A small cross-sectional study reported a positive association between PbB and increased systolic and diastolic blood pressure in women with pre-eclampsia (Disha et al. 2019).

Atherosclerosis. Few studies have evaluated associations between PbB ≤10 µg/dL and atherosclerosis (Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004). Studies are briefly summarized in Table 2-9, with additional details provided in the *Supporting Document for Epidemiological Studies for*

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Lead, Table 3. Ari et al. (2011) reported a positive correlation between PbB and intimal medial thickening of the greater carotid artery in non-diabetic hemodialysis patients at a concurrent PbB of 0.41 µg/dL. Peripheral artery disease was positively associated with PbB levels ≥ 2.47 µg/dL, with a positive trend across quartiles, in a study of a large NHANES 1999–2002 (age 18 years or older) population (Muntner et al. 2005), whereas analyses restricted to adult (≥ 40 years old) participants of NHANES 1999–2000 reported a positive trend for the risk of peripheral artery disease, although ORs for PbB quartiles (highest PbB quartile > 2.90 µg/dL) were not associated with peripheral artery disease (Navas-Acien et al. 2004).

Cardiac function and heart disease. Several studies have investigated cardiac function and heart disease, including a series of studies conducted in men from the Normative Aging Study in the greater Boston, Massachusetts area that evaluated associations between PbB ≤ 10 µg/dL and alterations in cardiac conduction and ischemic heart disease (Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a). Studies are briefly summarized in Table 2-10, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies on the Normative Aging Study population show positive associations between bone Pb concentrations (at concomitant PbB ≤ 10 µg/dL) and changes to electrocardiograms (prolonged QT and QRS intervals) and atrioventricular conduction defect; however, no associations were observed between PbB and conduction abnormalities (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a). For ischemic heart disease, increased risks were associated with PbB and with tibia and patella Pb concentrations (Jain et al. 2007). A 1 SD increase in PbB was associated with a 1.27-fold increase in risk for ischemic heart disease (Jain et al. 2007). In addition to the evaluations of the Normative Aging Study population, a large cross-sectional study of 2,163 men and 3,185 women found an increased risk of cardiovascular disease (including coronary artery disease, myocardial infarction, and stroke) for women in the two highest exposure PbB quartiles (Q3: 3.77–5.460 µg/dL; Q4: ≥ 5.461 µg/dL), although risk was not increased for men in any PbB quartile (Q4: ≥ 6.25 µg/dL) (Chen et al. 2017). Other studies have evaluated left ventricular function and structure, heart rate variability, and QRS-T wave angle (Jing et al. 2019; Yang et al. 2017; Yu et al. 2019a). A small (n=179) prospective study in adults with a mean PbB of 4.18 µg/dL showed an inverse association between PbB and left ventricular systolic function, but not left ventricular diastolic function or left ventricular structure (Yang et al. 2017). Results of a small (n=328) cross-sectional study in newly hired male Pb workers did not observe an association between PbB (mean 4.54 µg/dL) and heart rate variability (Yu et al. 2019a). A large (n=7,179) study of NHANES III participants showed that PbB was associated

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Table 2-9. Summary of Epidemiological Studies Evaluating Atherosclerosis at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Ari et al. 2011	Mean	Greater carotid artery intima-media thickness	β (SE), mm per µg/dL PbB: 0.101 (0.040); p=0.013*
Clinical study; n=50 adult male and female hemodialysis patients and 48 age- and sex-matched controls	<ul style="list-style-type: none"> Hemodialysis patients: 0.41 Controls: 0.10 		
Muntner et al. 2005^c	Mean: 1.64 Quartiles:	PAD	OR for prevalence in Q4: 1.92 (1.02–3.61)* p-trend (across quartiles): <0.001*
Cross-sectional study; n=9,961 participants	<ul style="list-style-type: none"> Q1: <1.06 Q2: 1.06–1.63 Q3: 1.63–2.47 Q4: ≥2.47 		
Navas-Acien et al. 2004^c	Mean: 2.07 Quartiles:	PAD	OR for prevalence in Q4: 2.88 (0.87, 9.47) p-trend (across quartiles) for risk: 0.02*
Cross-sectional study; n=2,125 participants	<ul style="list-style-type: none"> Q1: <1.45 Q2: 1.45–2.07 Q3: 2.07–2.90 Q4: >2.90 		

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 3 for more detailed descriptions of studies.^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs^cStudy population was from NHANES.

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PAD = peripheral artery disease; pb = lead; SE = standard error

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Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^{b,c}
Chen et al. 2017		Cardiovascular disease	ORs: Men, Q4: 1.01 (0.58, 1.78); p-trend: 0.59 Women, Q3: 1.65 (1.03, 2.66)* Women, Q4, 1.93 (1.22, 3.04); p-trend: <0.01*
Cross-sectional study; n=5,348 adults (men: 2,163; women: 3,185) aged ≥ 18 years	<ul style="list-style-type: none"> Quartiles: <ul style="list-style-type: none"> Men <ul style="list-style-type: none"> Q1: ≤ 2.900 Q2: 2.901–4.400 Q3: 4.401–6.248 Q4: ≥ 6.249 Women <ul style="list-style-type: none"> Q1: ≤ 2.50 Q2: 2.501–3.770 Q3: 3.771–5.460 Q4: ≥ 5.461 		
Cheng et al. 1998^d		QT interval	β , msec per 10-fold increase in PbB: -0.65 (-10.40, 9.10); p=0.90 β, msec per 10-fold increase in tibia Pb: 5.03 (0.83, 9.22); p=0.02* β, msec per 10-fold increase in patella Pb: 3.00 (0.16, 5.84); p=0.04*
Longitudinal study; n=775 men (n=277 for men <65 years of age)	<ul style="list-style-type: none"> PbB mean: 5.8 Bone Pb, $\mu\text{g}/\text{g}$, mean (SD) <ul style="list-style-type: none"> Tibia: 22.2 (13.4) Patella: 30.8 (19.2) 	QRS interval	β , msec per 1 unit increase in PbB: -3.49 (-10.72, 3.75); p=0.35 β, msec per 1-fold increase in tibia Pb: 4.83 (1.83, 7.83); p<0.01* β, msec per 1-fold increase in patella Pb: 2.23 (0.10, 4.36); p=0.04*
		IVCD	OR for a 10-fold increase in tibia Pb: 2.23 (1.28, 3.90); p<0.01*

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Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^{b,c}
Eum et al. 2011^d	PbB baseline mean: 5.8	QT interval	PbB OR for T3: 1.31 (0.69, 2.48); p-trend: 0.41
Prospective longitudinal study; n=600 men	PbB Tertiles: • T1: <4 • T2: 4–6 • T3: >6 Tibia Pb ($\mu\text{g}/\text{g}$) baseline mean: 21.6 Tertiles: • T1: <16 • T2: 16–23 • T3: >23		Tibia OR for T3: 2.53 (1.22, 5.25)*; p-trend: 0.003*
		Atrioventricular conduction defect	PbB OR for T3: 0.52 (0.19, 1.45); p-trend: 0.16 Tibia OR for T3: 0.23 (0.06, 0.87); p-trend: 0.03
Jain et al. 2007^d	PbB baseline mean • Non-cases 6.2 • Cases 7.0 Patella Pb ($\mu\text{g}/\text{g}$) baseline mean • Non-cases 30.6 • Cases 36.8	Ischemic heart disease	PbB β per 1 SD increase in PbB: 1.27 (1.01, 1.59)* PbB HR per 1 log increased in PbB: 1.45 (1.01, 2.06); p=0.05* Patella Pb HR per 1 log increased in bone Pb: 2.64 (1.09, 6.37); p=0.05*
Park et al. 2009a^d	PbB median (IQR): 5 (4–7) Patella Pb ($\mu\text{g}/\text{dL}$), median (IQR): 26 (18–37) Tibia Pb ($\mu\text{g}/\text{dL}$), median (IQR): 19 (14–27)	QT interval	PbB β for msec increase per IQR: 1.3 (-0.76, 3.36) Patella β for msec increase per IQR: 2.64 (0.13, 5.15)* Tibia β for msec increase per IQR: 2.85 (0.29, 5.40)*
Yang et al. 2017	PbB baseline Gmean: 4.19	Left ventricular systolic function	β , per doubling of PbB for ejection fraction (%): 0.150 (-1.019, 1.320); p=0.800 β, per doubling of PbB for global longitudinal strain (%): -0.392 (-0.753, -0.030); p=0.034* β, per doubling of PbB for regional longitudinal strain (%): -0.618 (-1.167, -0.068); p=0.028*

Prospective study; n=179 adults (50.3% women); follow-up period 11.9 years

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Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^{b,c}
Yu et al. 2019a Cross-sectional study; n=328 newly hired male Pb workers	Mean: 4.54	β, per doubling of PbB for regional longitudinal strain rate (per second): -0.056 (-0.097, -0.015); p=0.008*	
		β , per doubling of PbB for regional radial strain (%): -1.825 (-3.740, 0.090); p=0.062	
		β, per doubling of PbB for regional radial strain rate (per second): -0.113 (-0.226, -0.0002); p=0.050*	
		β , per doubling of PbB for left ventricular mass (g/m^2): -1.399 (-4.504, 1.707); p=0.375	
		β , per doubling of PbB for end-diastolic diameter (cm): -0.064 (-0.134, 0.006); p=0.072	
		β , per doubling of PbB for relative wall thickness: 0.0065 (-0.0031, 0.0162); p=0.185	
		Heart rate variability	Regression (β) coefficients (95% CI) per 10-fold increase in PbB: <ul style="list-style-type: none"> • Supine position: 3.0 (-20.4, 33.0); p=0.82 • Standing position: -6.0 (-26.2, 19.7); p=0.61 • Orthostatic change: -8.8 (-31.8, 17.5); p=0.47

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 3 for more detailed descriptions of studies.^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.^cIf bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤ 10 $\mu\text{g}/\text{dL}$.^dStudy population was from the Normative Aging Study.

CI = confidence interval; Gmean = geometric mean; HR = hazard ratio; IQR = intraquartile range; IVCD = intraventricular conduction defect; OR = odds ratio; Pb = lead; SD = standard deviation

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with an abnormal QRS-T wave angle in men (mean PbB: 4.10 µg/dL), but not in women (mean PbB: 2.93 µg/dL) (Jing et al. 2019).

Mortality due to cardiovascular disease. Mortality due to cardiovascular disease at PbB ≤10 µg/dL has been examined in large prospective and longitudinal studies, which provide mixed results. Studies are briefly summarized in Table 2-11, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Three of these were conducted in large studies of men and women participating in NHANES (Aoki et al. 2016; Lanphear et al. 2018; Menke et al. 2006; Schober et al. 2006). Aoki et al. (2016), Lanphear et al. (2018), and Menke et al. (2006) observed positive associations of mortality due to cardiovascular disease, including ischemic heart disease, myocardial infarction, and stroke and at PbB ≤10 µg/dL, including positive trends for mortality with increasing PbB.

In contrast, Schober et al. (2006) did not find increased cardiovascular mortality risk at PbB <10 µg/dL, although risk was increased at PbB ≥10 µg/dL and a positive trend for mortality was observed with increasing PbB. For PbB, no increased risk or positive trend for mortality due to cardiovascular was observed in men from the Normative Aging Study (Weisskopf et al. 2009). In women, the risk of mortality due to coronary heart disease was increased at PbB ≥8 µg/dL compared to PbB <8 µg/dL (Khalil et al. 2009).

Associations Between Bone Pb and Cardiovascular Effects. Several studies have evaluated associations between bone Pb concentration and blood pressure and cardiac outcomes. Results provide evidence that long-term exposure to Pb produces adverse effects on the cardiovascular system.

Increased blood pressure and hypertension. Numerous studies show associations between bone Pb concentration and increased blood pressure and increased risk of hypertension (see Table 2-12). The most studied population is older men participating in the Normative Aging Study. Results consistently show positive associations between tibia Pb and systolic blood pressure (Cheng et al. 2001), pulse pressure (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010), and risk of hypertension (Cheng et al. 2001; Elmarsafawy et al. 2006; Hu et al. 1996a; Peters et al. 2007). The association between bone Pb and elevated pulse pressure suggests that Pb may alter cardiovascular function through loss of arterial elasticity (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010). Associations between patella Pb and blood pressure outcomes have been somewhat less consistent, with some studies showing positive associations (Hu et al. 1997; Jhun et al. 2015; Perlstein et al. 2007; Peters et al. 2007; Zhang et al. 2010) and other studies showing no associations (Cheng et al. 2001; Elmarsafawy et al. 2006). Other study

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Table 2-11. Summary of Epidemiological Studies Evaluating Mortality due to Cardiovascular Disease at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Aoki et al. 2016^c Prospective study; n=18,602	Mean: 1.73	Mortality due to cardiovascular disease	RR, per 10-fold increase in PbB: 1.44 (1.05, 1.98)*
Khalil et al. 2009 Prospective study; n=533 women	Mean: 5.3	Mortality due to coronary heart disease	PbB ≥8.0 compared to women with PbB <8.0. HR: 3.08 (1.23, 7.70); p=0.016*
Menke et al. 2006^c Longitudinal study; n=13,946	Baseline mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.63	Mortality due to cardiovascular disease Mortality due to myocardial infarction Mortality due to stroke	HR for T3 versus T1: 1.55 (1.08, 2.24)*; p-trend: 0.003* HR for T3 versus T1: 1.89 (1.04, 3.43)*; p-trend: 0.007* HR for T3 versus T1: 2.51 (1.20, 5.26)*; p-trend: 0.017* RR for T3 versus T1: 1.55 (1.16, 2.07)*; p-trend: <0.01*
Lanphear et al. 2018^c Longitudinal study; n=14,289	Mean: 2.71	Mortality due to cardiovascular disease Mortality due to ischemic heart disease	HR for PbB increase from 1.0 to 6.7 µg/dL: 1.70 (1.30, 2.22)* HR for PbB increase from 1.0 to 6.7 µg/dL: 2.08 (1.52, 2.85)*
Weisskopf et al. 2009^d Longitudinal study; n=868 men	Mean: 5.6 Tertiles • T1: <4 • T2: 4–6 • T3: >6	Mortality due to cardiovascular disease	HR for T3 versus T1: 1.10 (0.67, 1.80); p-trend: 0.72

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 3 for more detailed descriptions of studies.^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.^cStudy population was from NHANES.^dStudy population was from the Normative Aging Study.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; Pb = lead; RR = risk ratio

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populations examined include adults (Martin et al. 2006), young adults (Gerr et al. 2002), current and former Pb workers (Glenn et al. 2003; Lee et al. 2001), women (Korrick et al. 1999), pregnant women (Rothenberg et al. 2002), and mother-child pairs (Zhang et al. 2011). Although study results are not consistent, positive associations between bone Pb and blood pressure and risk of hypertension have been reported. Navas-Acien et al. (2008) conducted a meta-analysis of 10 studies (see Table 2-12 for studies included in the analysis) to evaluate associations between tibia and patella Pb and blood pressure outcomes. Positive associations were observed between tibia Pb and systolic blood pressure and hypertension risk, but no associations were observed between tibia Pb and diastolic blood pressure or between patella Pb and systolic blood pressure, diastolic blood pressure, or hypertension risk.

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Cheng et al. 2001 ^a	833 men ^b	↑ T 0 P	–	–	↑ T 0 P
Elmarsafawy et al. 2006	471 men ^b	–	–	–	↑ T (at low dietary calcium) 0 P (at high dietary calcium)
Gerr et al. 2002 ^a	508 young adults ^c	↑ T	↑ T	–	–
Glenn et al. 2003 ^a	496 male Pb workers ^d	↑ T ↑ P	0 T 0 P	–	–
Glenn et al. 2006 ^a	575 adult Pb workers ^e	↓ T	0 T	–	–
Hu et al. 1996a ^a	590	–	–	–	↑ T ↑ P
Jhun et al. 2015	727 men ^b	–	–	↑ T ↑ P	–
Korrick et al. 1999 ^a	689 women (214 cases; 475 controls) ^f	–	–	–	0 T ↑ P
Lee et al. 2001 ^a	924 adult Pb workers (789 cases; 135 controls) ^e	↑ T	0 T	–	↑ T
Martin et al. 2006 ^a	964 adults	0 T	0 T	–	↑ T
Perlstein et al. 2007	593 men ^b	–	–	↑ T ↑ P	–

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Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Peters et al. 2007	512 men ^b	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002 ^a	1,006 pregnant women	–	–	–	↑ C (3 rd trimester) 0 T (3 rd trimester)
Schwartz et al. 2000c ^a	543 male Pb workers ^d	0 T	0 T	–	0 T
Weaver et al. 2008	652 Pb workers ^e	0 P	0 P	–	0 P
Zhang et al. 2010	612 men ^b	–	–	↑ T ↑ P	–
Zhang et al. 2011	457 mother-child pairs ^g	↑ T (girls) 0 T (boys)	↑ T (girls) 0 T (boys)	–	–

^aIncluded in the Navas-Acien et al. (2008) meta-analysis.^bParticipants in the Normative Aging Study.^c19–29 years of age.^dCurrent and former Pb workers in the United States.^eCurrent and former Pb workers in South Korea.^fNurses Health Study.^gBased on maternal bone Pb measurement.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; C = calcaneus bone; P = patella; Pb = lead; T = tibia

Cardiac function. Several studies evaluating associations between bone Pb and cardiac function, disease, and mortality were conducted in participants of the Normative Aging Study (see Table 2-13). For tibia Pb, positive associations have been observed for QT and QRS intervals (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a), atrioventricular and intraventricular block (Cheng et al. 1998), and ischemic heart disease (Jain et al. 2007). For patella Pb, positive associations were observed for QT and QRS intervals (Cheng et al. 1998; Park et al. 2009a). Both tibia Pb and patella Pb were positively associated with ischemic heart disease (Jain et al. 2007), and patella and tibia Pb were associated with an increased risk of coronary heart disease (Ding et al. 2016, 2019). However, no association was observed between tibia or patella Pb and all cardiovascular mortality or mortality due to ischemic heart disease (Weisskopf et al. 2009).

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Table 2-13. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

Reference	Population	Outcome		
		Function	Disease	Mortality
Cheng et al. 1998	775 men ^a	↑ T (QT and QRS intervals; AV block; IV block) ↑ P (QT and QRS intervals) 0 P (AV block; IV block)	–	–
Ding et al. 2016	589 men ^a	–	↑ P (CHD)	–
Ding et al. 2019	594 men ^a	–	↑ T (CHD) ↑ P (CHD)	–
Eum et al. 2011	600 men ^a	↑ T (QT and QRS intervals) 0 P (QT and QRS intervals)	–	–
Jain et al. 2007	837 men ^a	–	↑ T (IHD) ↑ P (IHD)	–
Park et al. 2006	413 men ^a	0 T (HRV with MetS) 0 T (HRV without MetS) ↑ P (HRV with MetS) 0 P (HRV without MetS)	–	–
Park et al. 2009a	613 men ^a	↑ T (QT interval) ↑ P (QT interval)	–	–
Weisskopf et al. 2009	868 men ^a	–	–	0 T (all cardiovascular or IHD deaths) 0 P (all cardiovascular or IHD deaths)

^aParticipants in the Normative Aging Study.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; AV = atrioventricular; CHD = coronary heart disease; HRV = heart rate variability; IHD = ischemic heart disease (defined as myocardial infarction or angina pectoris); IV = intraventricular; MetS = metabolic syndrome (three or more of the following: obesity, diabetes, hypertension, and dyslipidemia); P = patella; Pb = lead; T = tibia

Mechanisms of Action. Several studies and recent reviews include discussions of mechanisms that may be involved in Pb-induced effects on cardiovascular function (Faramawai et al. 2015; Ghiasvand et al. 2013; Mitra et al. 2017; Nawrot et al. 2002; Shiue et al. 2014; Weisskopf et al. 2009; Xu et al. 2015; Zota et al. 2013). Control of cardiovascular function is multi-factorial; therefore, numerous mechanisms are likely involved in Pb-induced cardiovascular effects. Specific mechanisms for cardiovascular effects include: impairment of renal function; effects on vascular smooth muscle, including constrictive effects and disruption of NO-induced vasodilatory actions; increase of sympathetic nervous system activity;

altered chemoreceptor activity; and altered regulation of the renin-angiotensin-aldosterone axis and the renal kallikrein system. In addition, general mechanisms of toxicity of Pb, including oxidative stress, inflammation, and altered transport of ions across cellular membranes, also are likely to be involved (see Section 2.21).

2.7 GASTROINTESTINAL

Overview. Few epidemiological studies have evaluated gastrointestinal effects associated with chronic exposure to Pb. Almost all available studies were conducted in small numbers of workers with PbB >10 $\mu\text{g/dL}$, although one study included a group of workers with PbB ≤ 10 $\mu\text{g/dL}$. Study results consistently show gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from 8.04 $\mu\text{g/dL}$ to approximately 100 $\mu\text{g/dL}$. As reviewed in Section 2.2 (Acute Lead Toxicity), acute exposure to Pb is associated with gastrointestinal symptoms and intestinal paralysis.

The following gastrointestinal effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Gastrointestinal symptoms (abdominal colic/discomfort).
- >10 $\mu\text{g/dL}$:
 - Gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea and/or constipation); corroborated in a few studies.

Measures of Exposure. Studies examining the association between gastrointestinal effects of Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies on gastrointestinal effects of Pb are survey or cross-sectional studies of small populations of workers. In general, studies did not consider factors, such as age, diet, nutritional factors, alcohol use, and potential exposure to other occupational chemicals or limitations such as study design (cross-sectional and survey). Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

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Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few epidemiological studies have investigated the gastrointestinal effects of chronic exposure to Pb (see Table 2-14). With the exception of a survey study conducted in 497 workers (Rosenman et al. 2003), studies were conducted in small worker populations (n=69–155). Increased gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) were observed in all studies. The lowest PbB associated with increased gastrointestinal symptoms showed an increased percentage of workers reporting abdominal colic and discomfort at a mean PbB of 8.04 µg/dL, compared to controls (PbB 5.76 µg/dL) (Kuruvilla et al. 2006). For example, 18.9% of painters reported abdominal colic compared to 0 in the control group.

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Kuruvilla et al. (2006).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of gastrointestinal toxicity. EPA (2014c) specifically noted that oxidative stress through ROS could result in gastrointestinal toxicity; as a result, damage to the intestinal mucosa epithelium is possible.

2.8 HEMATOLOGICAL

Overview. Pb-induced toxicity to the hematological system has long been established. Pb inhibits heme synthesis, leading to the development of microcytic, hypochromic anemia. Numerous epidemiological studies have evaluated hematological effects associated with exposure to Pb in adults and children. Most studies were cross-sectional in design and evaluated effects on heme synthesis and subsequent changes in erythrocyte hemoglobin parameters and anemia. Studies in adults (general populations and workers) and children consistently show inhibition of heme synthesis enzymes, particularly δ-ALAD, and subsequent decreases in blood hemoglobin, red blood cell parameters (e.g., mean cell hemoglobin, mean cell volume), and development of anemia. Other hematological effects observed in epidemiological studies include alterations in erythrocyte function (decreased activities of pyrimidine 5'-nucleotidase and membrane Ca²⁺/Mg²⁺ ATPase), changes in serum EPO concentration, and decreased platelet count.

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Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB ($\mu\text{g/dL}$)	Outcomes evaluated ^a	Effects ^b
Awad el Karin et al. 1986 Cross-sectional study; n=92 exposed; 40 controls	Range of means (by job category): 48.1–80.7 Controls mean: 21.2	Abdominal colic	<ul style="list-style-type: none"> Exposed (% reporting symptom) 41.3; exposed versus control p=0.01* Control (% reporting symptom): 7.5
		Constipation	<ul style="list-style-type: none"> Exposed (% reporting symptom) 41.4; exposed versus control p=0.01* Control (% reporting symptom): 10.0
Baker et al. 1979 Survey study; n=160 Pb workers	Range of means (by job category): 41.8–87.2	Gastrointestinal symptoms	<ul style="list-style-type: none"> Mean PbB at which symptoms are present: 101.24 $\mu\text{g/dL}$ (p<0.01)* PbB, symptom absent: 65.98 $\mu\text{g/dL}$
		Abdominal pain	<ul style="list-style-type: none"> PbB, symptoms present: 100.77 $\mu\text{g/dL}$ (p<0.01)* PbB, symptom absent: 68.25 $\mu\text{g/dL}$
Kuruvilla et al. 2006 Cross-sectional study; n=155; exposed workers: n=105 (52 battery workers; 53 painters); controls: n=50	Mean <ul style="list-style-type: none"> Battery workers: 42.40 Painters: 8.04 Controls: 5.76 	Abdominal colic	<ul style="list-style-type: none"> Battery workers (% reporting symptom): 17.3; p<0.01* Painters (% reporting symptom): 18.9; p<0.01* Controls (% reporting symptom): 0
		Abdominal discomfort	<ul style="list-style-type: none"> Battery workers (% reporting symptom): 19.2; p<0.01* Painters (% reporting symptom): 26.4; p<0.001* Controls (% reporting symptom): 2
		Vomiting	<ul style="list-style-type: none"> Battery workers (% reporting symptom): 1.9 Painters (% reporting symptom): 1.9 Controls (% reporting symptom): 0
		Constipation	<ul style="list-style-type: none"> Battery workers (% reporting symptom): 0 Painters (% reporting symptom): 1.9 Controls (% reporting symptom): 2

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Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated ^a	Effects ^b
Matte et al. 1989	<ul style="list-style-type: none"> • Mean: not reported • Workers stratified by PbB <60 and ≥60 	Nausea	<ul style="list-style-type: none"> • PbB <60 (% reporting symptom): 7 • PbB ≥60 (% reporting symptom): 14 • PR (95% CI): 2.0 (0.5, 7.9)
Survey study; n=69 (46 manufacturing and 23 battery repair workers)		Abdominal pain	<ul style="list-style-type: none"> • PbB <60 (% reporting symptom): 12 • PbB ≥60 (% reporting symptom): 18 • PR (95% CI): 1.5 (0.5, 4.6)
Rosenman et al. 2003	<ul style="list-style-type: none"> • Range 10–70 • Stratification by PbB: <ul style="list-style-type: none"> ◦ 10–24 (n=139) ◦ 25–29 (n=98) ◦ 30–39 (n=171) ◦ 40–49 (n=58) ◦ 50–59 (n=22) ◦ ≥60 (n=9) 	Abdominal pain	AdjOR (95% CI) for PbB: <ul style="list-style-type: none"> • 10–24: 1 (reference) • 25–29: 0.62 (0.28, 1.37) • 30–39: 0.98 (0.53, 1.82) • 40–49: 2.15 (1.03, 4.49)* • 50–59: 1.54 (0.52, 5.23) • ≥60: NR
Survey study; n=497 workers			

^aGastrointestinal symptoms include abdominal colic, nausea, vomiting, diarrhea, and/or constipation.^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

AdjOR = adjusted odds ratio (adjusted by age, ethnicity group, company screening, and smoking status); CI = confidence interval; NR = not reported; PbB = blood lead concentration; PR: prevalence ratio

The following hematological effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Inhibition of δ -ALAD; demonstrated in a few studies.
 - Decreased blood hemoglobin; evaluated in several studies with mixed results.
 - Decreased platelet count.
 - Decreased plasma EPO in adult males.
- > 10 $\mu\text{g/dL}$:
 - Dose-dependent decreased heme synthesis due to inhibition of δ -ALAD and other heme metabolism enzymes; demonstrated in numerous studies.
 - Anemia and decreased blood hemoglobin; demonstrated in numerous studies.
 - Decreased activity of other erythrocyte enzymes (pyrimidine 5'-nucleotidase or red blood cell membrane $\text{Ca}^{2+}/\text{Mg}^{2+}\text{ATPase}$); demonstrated in a few studies.
 - Altered plasma EPO concentration:
 - Decreased in adult males; evaluated in a few studies with mixed results.
 - Decreased in pregnant females; demonstrated in one study, but findings not corroborated.
 - Mixed results (both increases and decreases observed) in children; evaluated in a few studies.

Measures of Exposure. Studies evaluating the association between hematological effects and Pb exposure most commonly evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. In general, available epidemiological studies on hematological effects do not control for factors, including concomitant exposure to other chemicals, that may affect the hematological system. In addition, dietary insufficiency of iron is the primary cause of microcytic, hypochromic anemia; however, few studies evaluated this as an effect modifier. Age and renal function are also confounding factors, as impairment of renal function can affect renal EPO synthesis and PbB. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. General trends for studies showing a relationship between PbB and hematological effects are shown in Table 2-15. Most epidemiological studies of hematological effects have examined effects on heme metabolism and its consequences, with fewer studies examining other

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hematological endpoints (altered serum levels of EPO, altered erythrocyte function, and decreased platelet count). As noted above, Pb-induced toxicity to the hematological system, specifically inhibition of heme synthesis enzymes and resulting anemia and decreased erythrocyte hemoglobin, have long been established. Numerous epidemiological studies in adults and children provide consistent evidence that δ -ALAD activity is inversely correlated with PbB over a PbB range of <10 – >50 $\mu\text{g/dL}$ (see Table 2-15) with δ -ALAD inhibition and subsequent effects of inhibition showing concentration-dependence for PbB (Murata et al. 2009; Schwartz et al. 1990). A few studies have reported other hematological effects, including decreased platelet count in Pb workers at PbB of 5.4 $\mu\text{g/dL}$ (Conterato et al. 2013) and >41 $\mu\text{g/dL}$ (Barman et al. 2014). Inhibition of non-heme metabolism enzymes in erythrocytes was also associated with PbB. In Pb workers, membrane $\text{Ca}^{2+}/\text{Mg}^{2+}$ ATPase was inhibited at a PbB range of approximately 29–42 $\mu\text{g/dL}$ (Abam et al. 2008), and pyrimidine 5'-nucleotidase was inhibited at a PbB of >50 $\mu\text{g/dL}$ (Buc and Kaplan 1978). Pyrimidine 5'-nucleotidase also was inhibited in children (aged 1–5 years) with a PbB range of 30–72 $\mu\text{g/dL}$ (Angle et al. 1982).

Table 2-15. Overview of Hematological Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) ($\mu\text{g/dL}$)	Effects associated with Pb exposure	References
≤ 10	Altered heme synthesis ^a	Ahamed et al. 2006; Ergurhan-Ilhan et al. 2008; Wang et al. 2010
	Anemia and/or decreased measures of RBC hemoglobin ^b	Ahamed et al. 2006; Conterato et al. 2013; Olivero-Verbel et al. 2007; Queirolo et al. 2010; Riddell et al. 2007; Ukaejiofo et al. 2009
	Increased hemoglobin	Chen et al. 2019
	Decreased platelet count	Conterato et al. 2013
	Decreased EPO	Sakata et al. 2007
>10 – 30	Altered heme synthesis ^a	Ahamed et al. 2005, 2006; Counter et al. 2008, 2009; Grandjean and Lintrup 1978; La-Llave-Leon et al. 2017; Lauwerys et al. 1978; Mohammad et al. 2008; Murata et al. 2009; Piomelli et al. 1982; Rabinowitz et al. 1985; Roels et al. 1975, 1976; Roels and Lauwerys 1987; Schumacher et al. 1997; Stuik 1974
	Anemia and/or decreased measures of RBC hemoglobin ^b	Adebonojo 1974; Ahmed et al. 2007; Karita et al. 2005; Li et al. 2018; Schwartz et al. 1990; Shah et al. 2010
	Altered RBC function ^c	Abam et al. 2008; Huel et al. 2008
	Decreased platelet count	Barman et al. 2014
	Decreased EPO	Graziano et al. 1991, Liebelt et al. 1999

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Table 2-15. Overview of Hematological Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Increased EPO	Factor-Litvak et al. 1999;
>30–50	Altered heme synthesis ^a	Ademuyiwa et al. 2005; Alessio et al. 1976; Conterato et al. 2013; Fukumoto et al. 1983; Griffin et al. 1975; Murata et al. 2009; Roels et al. 1976; Secchi et al. 1974; Solliway et al. 1996
	Anemia and/or decreased measures of RBC hemoglobin ^b	Chwalba et al. 2018; Conterato et al. 2013; Dobrakowski et al. 2016; Schwartz et al. 1990; Solliway et al. 1996
	Altered RBC function	Abam et al. 2008; Angle et al. 1982; Buc and Kaplan 1978
	Increased reticulocytes	Kalahasthi and Barman 2016
	Decreased EPO	Romeo et al. 1996
	Increased EPO	Factor-Litvak et al. 1998; Graziano et al. 2004;
>50	Altered heme synthesis ^a	Cools et al. 1976; Gurer-Orhan et al. 2004; Jin et al. 2006; Meredith et al. 1978; Murata et al. 2009; Pagliuca et al. 1990; Schwartz et al. 1990
	Anemia and/or decreased measures of RBC hemoglobin ^b	Baker et al. 1979; Lilis et al. 1978; Malekirad et al. 2013; Grandjean 1979; Patil et al. 2006; Roels et al. 1979
	Decreased EPO	Romeo et al. 1996
	Altered RBC function ^c	Buc and Kaplan 1978

^aInhibition of heme synthesis measured by decreased δ -ALAD activity, elevated RBC levels or urinary levels of heme precursors (e.g., protoporphyrin, erythrocyte protoporphyrin, free erythrocyte protoporphyrin), and/or increased RBC zinc protoporphyrin/heme ratio.

^bDecreased blood hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and/or mean cell volume.

^cAltered erythrocyte function includes inhibition of pyrimidine 5'-nucleotidase or decreased RBC membrane $\text{Ca}^{2+}/\text{Mg}^{2+}$ ATPase.

ALAD = aminolevulinic acid dehydratase; EPO = serum erythropoietin; RBC = red blood cell

Several studies have evaluated the relationship between PbB and serum EPO levels in adults (Graziano et al. 1991; Osterode et al. 1999; Romeo 1996; Sakata et al. 2007) and children (Factor-Litvak 1998, 1999; Graziano et al. 2004; Liebelt et al. 1999). Erythropoietin is a glycoprotein hormone produced in renal proximal tubules that regulates steady-state and accelerated erythrocyte production. As a compensatory response to conditions producing low blood oxygen (e.g., anemia), proximal tubular cells release EPO, resulting in stimulated erythrocyte production. However, if renal function is compromised due to disease or toxicity (e.g., Pb-induced renal damage), the compensatory increases in serum EPO may be diminished or absent. Results of three cross-sectional studies in adult male workers are inconsistent, showing

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decreased serum EPO levels at PbB 6.4–65.1 µg/dL (Romeo et al. 1996; Sakata et al. 2007), but no effect on EPO at a PbB of 45.5 µg/dL (Osterode et al. 1999). Study populations in these cross-sectional studies were small (n for exposed groups=10–27). In a subgroup of 48 pregnant women (selected from a larger cohort of 1,502 pregnant women), serum EPO was decreased; the range of PbB means based on hemoglobin stratifications was 23.1–36.2 µg/dL (Graziano et al. 1991). Studies in children have yielded mixed results on associations between PbB and serum EPO. Results of a series of prospective studies of children (n=280) in former Yugoslavia indicate that serum EPO levels in Pb-exposed children exhibit age-dependence (Factor-Litvak et al. 1998, 1999; Graziano et al. 2004). Serum EPO was increased in children 4.5 (mean PbB: 39.3 µg/dL) and 6.5 years of age (mean PbB: 36.2 µg/dL), but not in children 9.5 (mean PbB: 28.1 µg/dL) or 12 years of age (mean PbB: 30.6 µg/dL) (Factor-Litvak et al. 1998, 1999; Graziano et al. 2004). The study authors suggested that the capacity for compensatory increases in EPO in response to Pb-induced anemia declines over time, possibly due to Pb-induced damage to the renal proximal tubule. In contrast to increases in EPO levels observed in the Yugoslavian cohort, Liebelt et al. (1999) showed decreased EPO levels in a group of children ages 1–6 years (n=95) who had a mean PbB of 18 µg/dL.

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies evaluating hematological effects of PbB ≤10 µg/dL are summarized in Table 2-16, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 4. Studies were conducted in small populations (n for exposed groups=25–391), except for two larger (n=855–2,861) cross-sectional studies in children (Liu et al. 2015a; Riddell et al. 2007). In general, studies show inverse associations between PbB ≤10 µg/dL and δ-ALAD activity and blood hemoglobin in adults and children, although results are mixed. Negative correlations between PbB and δ-ALAD activity (measured by plasma δ-ALAD activity or zinc protoporphyrin:heme ratio) have been observed in children (Wang et al. 2010), adolescent males (Ahamed et al. 2006), and adults (Wang et al. 2010) at mean PbB of 5.95–9.96 µg/dL; however, no effect on δ-ALAD activity was observed in children with a mean PbB of 7.11 µg/dL (Ahamed et al. 2005). Differences in δ-ALAD activity were observed for male automotive repair workers (mean PbB: 7.9 µg/dL) and male controls (mean PbB: 2.6 µg/dL). Additionally, two studies in adults showed that blood hemoglobin concentration was lower in Pb workers (mean PbB: 5.4–7.0 µg/dL) compared to controls (mean PbB: 1.5–3.0 µg/dL) (Conterato et al. 2013; Ukaejiofo et al. 2009). In contrast, blood hemoglobin and erythrocyte count were increased in adults living near an electronic waste site (median PbB 8.7 µg/dL), compared to controls (median PbB 8.7 µg/dL) (Chen et al. 2019). In children with mean

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Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^b
Heme metabolism			
Ahamed et al. 2005	Mean (SD)	δ -ALAD activity	No difference between groups:
Cross-sectional study; n=62 children (ages 4–12 years)	<ul style="list-style-type: none"> Group 1: 3.93 (0.61) Group 2: 7.11 (1.25) 		<ul style="list-style-type: none"> Group 1: 4.82 (1.25) Group 2: 4.56 (1.20)
Ahamed et al. 2006	Mean (SD): 9.96 (3.63) Range: 4.62–18.64	δ -ALAD activity	A negative correlation between PbB and blood δ-ALAD activity: $r = -0.592$; $p < 0.001$*
Cross-sectional study; n=39 adolescent males (ages 15–18 years)			
Ergurhan-Ilhhan et al. 2008	Mean (SD)	ALAD index	<ul style="list-style-type: none"> Controls: 0.40 (0.34) Workers: 0.73 (0.47); $p = 0.048$*
Cross-sectional study; n=25 male automotive repair workers (mean age 16.8 years); 24 male controls (mean age 16.3 years)	<ul style="list-style-type: none"> Controls: 2.6 (2.0) Workers: 7.9 (5.2) 	ZPP:heme ratio	<ul style="list-style-type: none"> Controls: 26.4 (7) Workers: 37.2 (15.9); $p = 0.045$*
Wang et al. 2010	Median	δ -ALAD activity	Pearson correlation coefficients:
Cross-sectional study; n=307 children (ages 4–13 years) and 391 adults (ages 16–77 years) from China	<ul style="list-style-type: none"> Children: 6.83 Adults: 5.95 		<ul style="list-style-type: none"> Children: -0.256; $p < 0.05$* Adults: -0.213; $p < 0.05$*
		ZPP	Pearson correlation coefficients:
			<ul style="list-style-type: none"> Children: 0.135; $p < 0.05$* Adults: 0.083; $p < 0.05$*
Blood hemoglobin/erythrocyte count			
Chen et al. 2019	Median (P_{25} , P_{75})	Hb	Median (P_{25} , P_{75}), g/dL
Cross-sectional study; n=158 exposed adults living near an electronic waste area (mean age: 44 years); n=109 controls (mean age: 47 years)	<ul style="list-style-type: none"> Control: 5.1 (3.9, 8.4) Exposed: 8.7 (6.2, 12.2) 		<ul style="list-style-type: none"> Control: 123.0 (107.0, 143.0) Exposed: 137.0 (119.5, 150.0), $p = 0.001$*
		Erythrocyte count	RBC count ($\times 10^3$), median (P_{25} , P_{75}):
			<ul style="list-style-type: none"> Control: 4.2 (3.5, 4.6) Exposed: 4.5 (4.1, 4.8), $p = 0.001$*

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Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^b
Conterato et al. 2013	Mean (SE)	Hb	Mean (SE), $\mu\text{g/dL}$
Cross-sectional study; n=50 painters; 36 controls	<ul style="list-style-type: none"> Control: 1.5 (0.1) Painters: 5.4 (0.4) 		<ul style="list-style-type: none"> Control: 15.4 (0.2) Painters: 15.0 (0.1); $p<0.05^*$
Liu et al. 2015a	PbB quartiles:	Hb	Change in Hb compared to Q1:
Cross-sectional study; n=855 children (age range: 3–7 years)	<ul style="list-style-type: none"> Q1: 2.20–5.16 Q2: 5.16–7.33 Q3: 7.33–10.62 Q4: 10.62–37.78 		<ul style="list-style-type: none"> PbB Q3: 1.45 (-0.28, 3.18) Erythrocyte Pb <ul style="list-style-type: none"> Q3: -3.01 (-4.71, 1.31); $p<0.05^{*,c}$ Q4: -3.97 (-5.68, -2.27); $p<0.05^*$
	Erythrocyte Pb quartiles:		
	<ul style="list-style-type: none"> Q1: 5.98–13.52 Q2: 13.52–19.35 Q3: 19.35–28.42 Q4: 28.42–101.01 		
Olivero-Verbel et al. 2007	Mean (SE): 5.49 (0.23)	Hb	Spearman correlation coefficient: 0.069; $p=0.348$
Cross-sectional study, n=189 children (age range 5–9 years)			
Queirolo et al. 2010	Mean (SD): 9.0 (6.0)	Hb	Blood Hb <10.5 g/L was a predictor of PbB; β (95% CI): 2.40 (0.77, 4.03); $p<0.01^*$
Cross-sectional study; n=222 children (age: 5–45 months)			
Riddell et al. 2007	Mean: 6.9	Hb	A 1 g/dL increase in Hb was associated with a 3% decrease in PbB ($p=0.043$) [*]
Cross-sectional study; n=2,861 children (age 6 months– 5 years)			
Ukaejiifo et al. 2009	Mean (SD)	Hb	Mean (SE), g/dL
Cross-sectional study; n=81 Pb workers; 30 controls	<ul style="list-style-type: none"> Controls: 3.00 (0.19) Workers: 7.00 (0.07) 		<ul style="list-style-type: none"> Controls: 12.96 (0.089) Workers: 12.05 (1.62); $p<0.001^*$

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Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

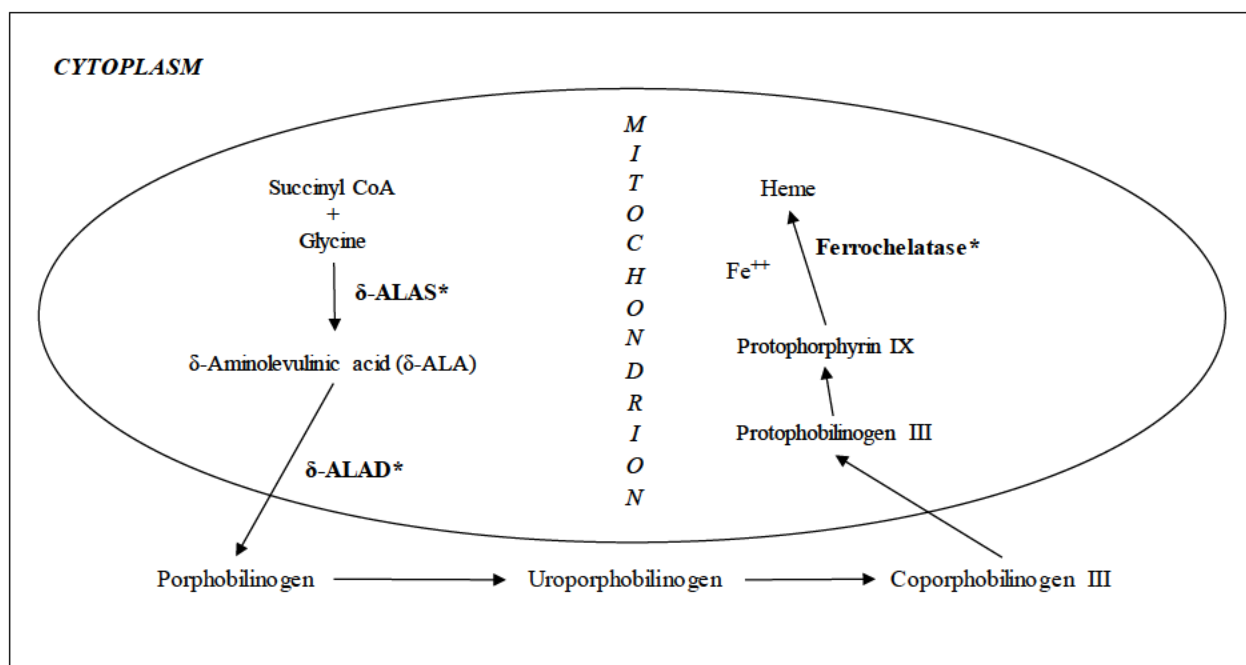
Reference and study population	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^b
Zentner et al. 2006	Umbilical mean (SD): 3.9 (3.6)	Hb	Pearson correlation coefficient: -0.04; $p=0.721$
Cross-sectional study; n=55 newborns			
Other hematological effects			
Conterato et al. 2013	Mean (SE)	Platelet count	Mean (SE), %
Cross-sectional study; n=50 painters; 36 controls	• Control: 1.5 (0.1)		• Control: 244.3 (8.3)
	• Painters: 5.4 (0.4)		• Painters: 203.7 (6.5); $p<0.05^*$
Sakata et al. 2007	Mean (SD); range	EPO	Mean (SD), mU/mL:
Cross-sectional studies: n=27 exposed workers; 9 controls	• Controls: 2.4 (1.1)		• Controls: 18.8 (4.6)
	• Workers: 6.4 (2.2)		• Workers: 12.7 (3.5); $p<0.01^*$

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 4 for more detailed descriptions of studies.^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.^cThe discrepancy between the 95% confidence limits and the p-value appears to be caused by an error in the reporting of the upper confidence limit (i.e., -1.31, rather than 1.31).ALAD index = $\log(\text{active } \delta\text{-ALAD}/\text{non-activated } \delta\text{-ALAD})$; $\delta\text{-ALAD}$ = δ -aminolevulinic acid dehydratase; CI = confidence interval; EPO = serum erythropoietin; Hb = hemoglobin; Pb = lead; SD = standard deviation; SE = standard error; ZPP = zinc-protoporphyrin

PbB of 6.9–9.0 µg/dL, there was an inverse association between blood hemoglobin concentrations and PbB (Queirolo et al. 2010; Riddell et al. 2007) and erythrocyte Pb concentration (Liu et al. 2015a). At lower PbB in newborns (PbB 3.9 µg/dL) and children (PbB 5.5 µg/dL), no correlation was found; however, these study populations were small (n=50–189) (Olivero-Verbel et al. 2007; Zentner et al. 2006). Thus, data are not adequate to establish an exposure-response relationship for decreased hemoglobin at PbB ≤10 µg/dL. Studies in small groups of workers (n=27–50) showed lower platelet count (PbB 5.4 µg/dL) and serum EPO concentrations (PbB 6.4 µg/dL) compared to controls (Conterato et al. 2013; Sakata et al. 2007). Although these findings have not been evaluated in other studies with PbB ≤10 µg/dL, similar effects have been observed at PbB >10 µg/dL.

Mechanisms of Action. Pb inhibits heme synthesis by inhibiting δ-ALAD and ferrochelatase (see Figure 2-4). As a consequence, the activity of the rate-limiting enzyme of the pathway, δ-aminolevulinic synthetase (δ-ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ-amino-levulinic acid (δ-ALA), increased blood and plasma δ-ALA, increased erythrocyte protoporphyrin (EP), and decreased hemoglobin. The impairment of heme synthesis by Pb may have a far-ranging impact not limited to the hematopoietic system. EPA (1986) provided an overview of the known and potential consequences of the reduction of heme synthesis as shown in Figure 2-5. Solid arrows indicate well-documented effects, whereas dashed arrows indicate effects considered to be plausible further consequences of the impairment of heme synthesis.

In addition to decreased hemoglobin synthesis, general mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of adverse effects to the hematological system. EPA (2014c) specifically noted effects of oxidative stress (altered antioxidant enzymes, decreased cellular glutathione, and lipid peroxidation) as an important mechanism for hematological effects. As reviewed in Section 3.2.3 (Toxicokinetics, Distribution), 99% of Pb in blood is distributed to erythrocytes, providing a toxicokinetic mechanism for hematological effects (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002).

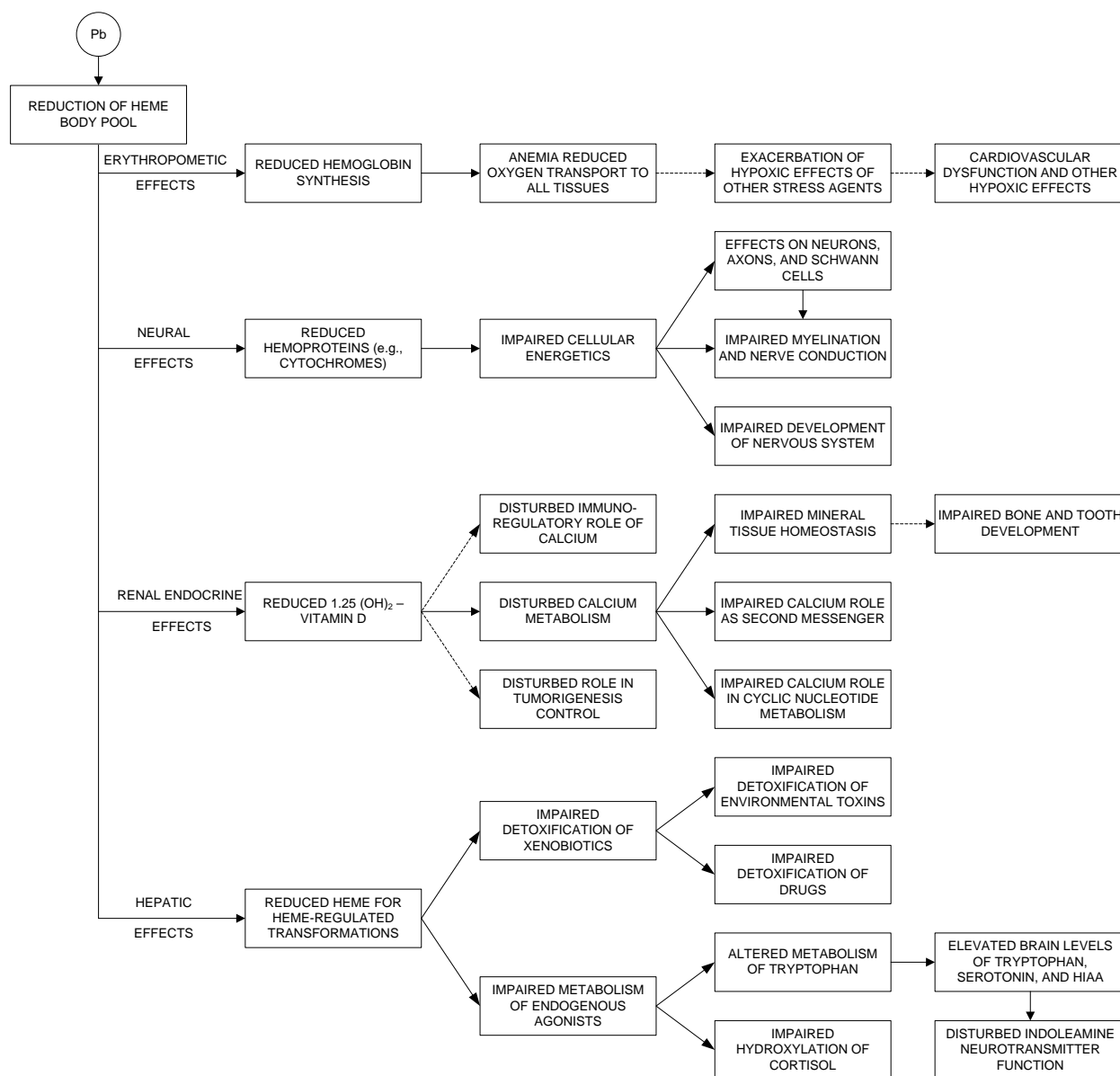
Figure 2-4. Pb Interactions in the Heme Synthesis Pathway

Abbreviations as noted in Ahamed and Siddiqui (2007): δ-ALAS = delta-aminolevulinic acid synthetase; δ-ALAD = delta-aminolevulinic dehydratase; CoA = coenzyme A

*Activity of enzymes inhibited by lead.

Source: Reprinted from Ahamed and Siddiqui (2007) with permission from Elsevier.

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Figure 2-5. Multiorgan Impact of Reduction of Heme Body Pool by Lead

Source: EPA 1986a

2.9 MUSCULOSKELETAL

Overview. Few epidemiological studies have evaluated musculoskeletal effects associated with Pb exposure; thus, limited data are available to fully describe the exposure-response relationship or evaluate the weight-of-evidence for certain effects. Studies provide evidence of bone loss, increased markers of bone metabolism/turnover, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries). However, within dose ranges (≤ 10 , 10–30, 30–50, and > 50 $\mu\text{g/dL}$),

few studies examined the same endpoints. Available studies include a prospective study in women and cross-sectional studies in adults and children, with some studies in large populations.

The following musculoskeletal effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Bone loss or markers of increased bone or joint tissue metabolism.
 - Periodontal bone loss.
 - Tooth loss.
 - Dental caries.
 - Periodontitis.
- > 10 $\mu\text{g/dL}$:
 - Muscle soreness/weakness.
 - Osteoporosis/decreased bone mineral density (BMD) in adults.
 - Increased BMD in children.
 - Periodontal disease.
 - Dental caries.

Measures of Exposure. Most studies examining the association between musculoskeletal effects and Pb exposure have evaluated exposure by measurement of PbB, although some studies also evaluated exposure by bone Pb concentration.

Confounding Factors and Effect Modifiers. A complicating factor in the interpretation of studies examining associations between PbB and bone loss or measures of bone metabolism is that increased bone metabolism (bone turnover or loss) can result in higher PbB due to Pb released from bone into the blood (reverse causality). This contributes to confounding from other factors that are associated with bone loss, including nutrition, age, pregnancy and menopause, and activity. Results of studies examining Pb-induced periodontal or dental effects need to account for dental hygiene, diet/nutrition, and previous dental interventions. For example, interpretation of results on associations between dental caries and PbB would be uncertain if daily fluoride intake or prophylactic dental treatments (e.g., fluoride treatments or coating of molars during childhood) were not considered as confounding factors. Studies that rely on *in vivo* estimates of bone Pb (e.g., XRF) as the exposure metric for changes in BMD should also consider the potential for changes in BMD affecting the measurement of the concentration of Pb in bone mineral (Hu et al. 2007).

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Characterization of Effects. Studies evaluating musculoskeletal effects associated with PbB provide evidence of bone loss, altered bone or joint tissue metabolism, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries). Due to the small number of studies, it is difficult to establish exposure-response relationships; in addition, within specific dose-ranges (≤ 10 , 10–30, 30–50, and > 50 $\mu\text{g/dL}$), few studies examined the same endpoints. Effects associated with chronic Pb exposure are shown in Table 2-17. In adults, decreased BMD has been observed over a PbB range of ≤ 10 – > 50 $\mu\text{g/dL}$ (Campbell and Auinger 2007; Dongre et al. 2013; Khalil et al. 2008; Lee and Park 2018), although BMD was not decreased in women at PbB ≤ 10 $\mu\text{g/dL}$ (Pollack et al. 2013). BMD was increased in a single study in children with a mean PbB of 23.6 $\mu\text{g/dL}$ (Campbell et al. 2004). The study authors suggested that the effect may represent accelerated bone maturation due to Pb-induced inhibition of parathyroid hormone-related peptide and transforming growth factor β -1. The study authors also noted that the accelerated bone maturation may be a predisposing factor for osteoporosis later in life. Sun et al. (2008a, 2008b) showed that PbB was associated with increased prevalence of osteoporosis (mean PbB men: 20.22 $\mu\text{g/dL}$; women 15.50 $\mu\text{g/dL}$). Periodontal disease (including periodontitis), periodontal bone loss, tooth loss, and dental caries have been reported over a PbB range of ≤ 10 –30 $\mu\text{g/dL}$ (Arora et al. 2009; Campbell et al. 2000a; Dye et al. 2002; Gemmel et al. 2002; Kim and Lee 2013; Kim et al. 2017a; Moss et al. 1999; Youravong and Teanpaisan 2015). Most studies examining periodontal and dental effects of Pb are conducted in populations with PbB ≤ 10 $\mu\text{g/dL}$. Muscle soreness and weakness has also been reported, although at higher PbB (40–49 $\mu\text{g/dL}$) (Rosenman et al. 2003).

Table 2-17. Overview of Musculoskeletal Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) ($\mu\text{g/dL}$)	Effects associated with Pb exposure	References
≤ 10	Bone loss/increased bone metabolism	Khalil et al. 2008; Lee and Park 2018; Machida et al. 2009; Nelson et al. 2009
	Tooth loss	Arora et al. 2009
	Periodontal bone loss	Dye et al. 2002
	Periodontitis	Kim and Lee 2013
	Dental caries	Gemmel et al. 2002; Kim et al. 2017a; Moss et al. 1999

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Table 2-17. Overview of Musculoskeletal Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>10–30	Osteoporosis	Sun et al. 2008a, 2008b
	Decreased bone mineral density (adults)	Campbell and Auinger 2007
	Increased bone mineral density (children)	Campbell et al. 2004
	Periodontal disease	Youravong and Teanpaisan 2015
	Dental caries	Campbell et al. 2000a
>30–50	Muscle soreness/weakness	Rosenman et al. 2003
	Decreased bone mineral density	Campbell and Auinger 2007
>50	Decreased bone mineral density	Dongre et al. 2013

Effects at Blood Pb Levels ≤10 µg/dL. Epidemiological studies of musculoskeletal effects associated with PbB ≤10 µg/dL have examined effects on bone and periodontal and dental health; studies are briefly summarized in Table 2-18, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 5. A prospective study in women reported an increased rate of bone loss at PbB ranges of 4–7 and 8–21 µg/dL and an increased risk of non-spine fractures at a PbB range of 8–21 µg/dL (Khalil et al. 2008). In cross-sectional studies, markers of bone metabolism were positively associated with PbB in women at mean PbBs of <2 and 2.9 µg/dL, although no relationship was observed for these markers and PbB in men (mean PbB: 1.2 µg/dL) (Machida et al. 2009; Nelson et al. 2011). In non-occupationally exposed men and women (n=443), PbB (mean 4.44 µg/dL) was negatively associated with BMD (Lee and Park 2018). However, no associations between PbB and BMD have been observed in cross-sectional studies in women at slightly lower PbB median PbB (1.8–2.2 µg/dL) (Machida et al. 2009; Pollack et al. 2013). Studies examining periodontal and dental effects include large (n=2,805–10,033) cross-sectional studies in adults and children (Dye et al. 2002; Kim and Lee 2013; Kim et al. 2017a; Moss et al. 1999). Positive associations have been observed between PbB and presence of dental furcations in male and female adults (mean PbB: 1.9–3.3 µg/dL) (Dye et al. 2002), periodontitis in adult males (PbB mean 3.1 µg/dL), but not females (mean PbB: 2.2) (Kim and Lee 2013), and dental

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Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^{b,c}
Bone metabolism			
Khalil et al. 2008	PbB:	Bone loss	Percentage rate of calcaneus bone loss
Prospective cohort study; n=533 women (age range: 65–87 years).	Mean (SD): 5.3 (2.3)		• T1: -1.01 (-1.27, -0.74)*
	Tertiles:		• T2: -1.41 (-1.57, -1.24)*
	• T1 (n=122): ≤ 3 (reference)		• T3: -1.49 (-1.86, -1.10)*; p=trend: 0.03
	• T2 (n=332): 4–7		
	• T3 (n=79): 8–21		
		Non-spine fractures	HR T3: 2.50 (1.25, 5.03)*; p-trend: 0.016
Lee and Park 2018	PbB:	BMD	Regression coefficient, β (SE), for BMD: -1.27 (0.48); p<0.01*
Cross-sectional study; n=443 adults (age range: 39–69 years)	Gmean: 4.44		
Machida et al. 2009	PbB:	BALP	Spearman's correlation coefficients
Cross-sectional study; n=1,225 female Japanese farmers (age range: 35–75 years)	Median		• All women: 0.143; p=0.000*
	• Premenopausal (n=261): 1.6		• Perimenopausal women: 0.234; p=0.000*
	• Perimenopausal (n=319): 2.0	OC	Spearman's correlation coefficients
	• Younger postmenopausal (n=397): 1.8		• All women: 0.191; p=0.000*
	• Older postmenopausal (n=248): 1.7	NTx	• Perimenopausal women: 0.391; p=0.000*
			Spearman's correlation coefficients
			• All women: 0.181; p=0.000*
			• Perimenopausal women: 0.261; p=0.000*
		BMD	Spearman's correlation coefficients
			• All women: -0.016; p=0.570
			• Perimenopausal women: -0.101; p=0.071

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Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^{b,c}
Nelson et al. 2011	Median (range)	uNTX-I	β , change in biomarker per 5 $\mu\text{g}/\text{dL}$ increase in In-PbB
Cross-sectional study; n=329 males (mean age: 65 years) and n=342 females (mean age: 62 years)	<ul style="list-style-type: none"> Males: 2.2 (0.5–25.1) Females: 1.9 (0.5–25.4) 	<ul style="list-style-type: none"> Males: 1.06 (0.95, 1.18) Females: 1.45 (1.21, 1.74)* 	
		uCTX-II	β , change in biomarker per 5 $\mu\text{g}/\text{dL}$ increase in In-PbB
		<ul style="list-style-type: none"> Males: 1.07 (0.97, 1.18) Females: 1.28 (1.04, 1.58)* 	
		C2C (65 years)	β , change in biomarker per 5 $\mu\text{g}/\text{dL}$ increase in In-PbB
		<ul style="list-style-type: none"> Males: 1.00 (0.94, 1.04) Females: 1.00 (0.92, 1.08) 	
		CP II	β , change in biomarker per 5 $\mu\text{g}/\text{dL}$ increase in In-PbB
		<ul style="list-style-type: none"> Males: 0.99 (0.93, 1.05) Females: 1.09 (0.97, 1.22) 	
		HA	β , change in biomarker per 5 $\mu\text{g}/\text{dL}$ increase in In-PbB
		<ul style="list-style-type: none"> Males: 1.01 (0.88, 1.05) Females: 0.96 (0.71, 1.29) 	
		COMP	β , change in biomarker per 5 $\mu\text{g}/\text{dL}$ increase in In-PbB
		<ul style="list-style-type: none"> Males: 1.08 (1.00, 1.18)* Females: 0.96 (0.87, 1.06) 	
Pollack et al. 2013	Mean (SD): 1.03 (0.64)	BMD	β per log-unit increase in PbB: 0.004 (-0.029, 0.020)
Cross-sectional study; n=249 premenopausal women (ages 18–44 years)			

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Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^{b,c}
Periodontal and dental effects			
Arora et al. 2009	PbB Tertiles	Tooth loss	OR PbB (compared to T1)
Cross-sectional study; n=333 men (age range: 50–94 years)	• T1: ≤ 4.0 (reference)		• T3: 0.88 (0.52, 1.50); p-trend=0.57
	• T2: 4.2–6.4		
	• T3: 7.0–35.0		OR Tibia Pb (compared to T1)
	Bone Pb ($\mu\text{g/g}$)		• T2: 1.81 (1.02, 3.18)*
	Tertiles for tibia		• T3: 3.03 (1.60, 5.76)*; p-trend=0.001*
	• T1: ≤ 15.0 (reference)		OR Patella Pb (compared to T1)
	• T2: 16.0–23.0		• T3: 2.41 (1.30, 4.49)*; p-trend 0.005*
	• T3: 24.0–96.0		
	Tertiles for patella		
	• T1: ≤ 22.0 (reference)		
	• T2: 23.0–36.0		
	• T3: 37.0–126.0		
Dye et al. 2002	Mean (SE)	Presence of dental furcations	β (SE), for presence of dental furcations
Cross-sectional study in 10,033 participants in NHANES III (ages 20–69 years)	• Males: 3.3 (0.12)		(combined men and women): 0.13 (0.05);
	• Females: 1.9 (0.05)		p=0.005*

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Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^{b,c}
Gemmel et al. 2002	Mean (SD)	Dental caries	Regression coefficient (SE):
Cross-sectional study in 498 children (age range: 6–10 years) from rural (n=239) and urban (n=259) settings.	<ul style="list-style-type: none"> Rural: 1.7 (1.0) Urban: 2.9 (2.0) 		<ul style="list-style-type: none"> Rural: -0.15 (0.09); p=0.09 Urban: -0.22 (0.08); p=0.005*
Kim and Lee 2013	PbB:	Periodontitis	OR (95% CI), per doubling of PbB:
Cross-sectional study; n=3,966 adults (≥ 20 years of age)	Mean (SE): <ul style="list-style-type: none"> Men <ul style="list-style-type: none"> no periodontitis: 2.625 (0.028) periodontitis: 3.118 (0.057); p<0.001 Women, <ul style="list-style-type: none"> no periodontitis: 1.906 (0.025) periodontitis: 2.222 (0.052); p<0.001 		<ul style="list-style-type: none"> Men: 1.699 (1.154, 2.503)* Women: 1.242 (0.833, 1.850)
Kim et al. 2017a	PbB:	Dental caries	PR for combined teeth with caries and filled teeth
Cross-sectional study; n=2,805 school-aged children (age range: ≤ 9 – ≥ 12 years)	Gmean: 1.53 Range: 0.11–4.89		<ul style="list-style-type: none"> Deciduous teeth: 1.14 (1.02, 1.27)* Permanent teeth: 0.83 (0.69, 0.99)

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Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^{b,c}
Moss et al. 1999	Mean (SE):	Dental caries in	OR per 5 $\mu\text{g}/\text{dL}$ increased in PbB: 1.8 (1.3, 2.5)*
Cross-sectional study;	• Age 2–5 years: 2.9	children (ages 5–	
n=24,901 participants (2–5 years old:	(0.12)	17 years)	
n=3,547; 6–11 years old: n=2,894;	• Age 6–11 years: 2.1		
≥ 12 years: n=18,460) in NHANES III	(0.08)		
	• Age 12–17 years:		
	2.5 (0.06)		

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 5 for more detailed descriptions of studies.

^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

^cIf bone Pb is noted under results, study did not show associations between PbB and musculoskeletal effects; however, results showed associations between bone Pb concentrations and musculoskeletal effects at concomitant PbB ≤ 10 $\mu\text{g}/\text{dL}$.

BALP = bone-specific alkaline phosphatase (marker of bone metabolism); BMD = bone mineral density; C2C = serum cleavage neopeptide of type II collagen (marker of joint tissue metabolism); CI = confidence interval; COMP = serum cartilage oligomeric matrix protein (marker of joint tissue metabolism); CPII = serum type II procollagen synthesis C-propeptide (marker of joint tissue metabolism); Gmean = geometric mean; HA = serum hyaluronic acid (marker of joint tissue metabolism); HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; NTx = N-telopeptide cross-linked collagen type I (marker of bone metabolism); OC = osteocalcin (marker of bone metabolism); OR = odds ratio; Pb = lead; PR = prevalence ratio; SD = standard deviation; SE = standard error; uCTX-II = C-telopeptide urine fragments of type II collagen (marker of joint tissue metabolism); uNTX-I = urine cross-linked N telopeptide of type I collagen (marker of joint tissue metabolism)

caries in children ages 6–17 years (PbB 2.1–2.4 µg/dL) (Moss et al. 1999). Kim et al. (2017a) reported that the prevalence of dental caries and filled teeth in children was increased for deciduous teeth, but not for permanent teeth; the mean PbB was 1.53 µg/dL, with all PbB <5 µg/dL. One study in adult males showed an association between bone Pb and tooth loss, but not PbB and tooth loss (Arora et al. 2009).

Mechanisms of Action. In bone and teeth, Pb substitutes for calcium (see Section 3.1.2, Toxicokinetics, Distribution). As reviewed by EPA (2014c) and Mitra et al. (2017), several mechanisms may be involved in the development of bone and periodontal/dental effects. Possible mechanisms include the following:

- Alterations in plasma growth hormones and calcitropic hormones (e.g., 1,25-[OH]₂D₃) leading to altered bone cell differentiation and function.
- Suppression in bone cell proliferation due to altered growth factors and hormones, including growth hormone, epidermal growth factor, transforming growth factor-beta 1 (TGF-β), and parathyroid hormone-related protein.
- Alterations in vitamin D-stimulated production of osteocalcin production, with inhibition of secreted bone-related proteins (e.g., osteonectin and collagen).
- Increased chondrogenesis through alterations of multiple signaling pathways, including TGF-β, bone morphogenic protein, activator protein-1, and nuclear factor kappa B.
- Inhibition of the post-eruptive enamel proteinases.
- Decreased microhardness of tooth surface enamel.

2.10 HEPATIC

Overview. Few epidemiological studies have evaluated hepatic effects associated with exposure to Pb, with most available studies comparing hepatic effects in small numbers of workers with PbB >10 µg/dL to controls with PbB lower than workers. Results of studies evaluating effects of Pb on liver function tests are inconsistent and do not demonstrate exposure-response relationships. Liver enlargement and increased gall bladder wall thickness was observed in workers with mean PbB of ≥28.66 µg/dL. Observed effects are consistent with oxidative stress. Histopathological effects of the liver associated with Pb have not been established.

The following hepatic effects have been associated with PbB >10 µg/dL:

- Greater plasma liver enzymes; evaluated in a few studies with mixed results.

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- Greater total cholesterol.
- Enlarged liver and increased thickness of gall bladder wall.

Measures of Exposure. Studies examining the association between hepatic effects Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies on hepatic effects of Pb were of small populations of workers using cross-sectional designs. In general, studies did not consider factors, such as age, diet, concurrent diseases, and potential exposure to other workplace chemicals that could affect hepatic function in association with, or independent of, Pb exposure. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few studies have investigated the hepatic effects of Pb. Brief study descriptions are provided in Table 2-19. Available studies were conducted in small populations (n=23–100) of workers with mean PbB of 5.4–77.5 µg/dL. The most serious effects reported for Pb-induced hepatic damage are liver enlargement and greater gall bladder wall thickness observed in workers with low PbB (28.66 µg/dL) and high PbB (40.58 µg/dL), respectively, compared to the control group (PbB 8.34 µg/dL) (Kasperczyk et al. 2013). However, these findings have not been corroborated in other studies. The study authors stated that no signs consistent with liver necrosis were observed. A cross-sectional study of a Chinese population evaluated the association between PbB and non-alcoholic fatty liver disease in China (Zhai et al. 2017). In women, a positive association between PbB and non-alcoholic fatty liver disease was observed in the two highest PbB quartiles (4.50–6.59 and >6.59 µg/dL; upper range not reported); no association was observed for men in the highest PbB quartile (>7.29 µg/dL; upper range not reported).

Most studies evaluated hepatic toxicity by liver function tests measuring plasma levels of liver enzymes. As shown in Table 2-20, results on effects of Pb on liver function tests are inconsistent and do not demonstrate exposure-response relationships. For example, Patil et al. (2007) reported greater alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in spray painters with a mean PbB of 22.32 µg/dL, but no change in ALT or AST in battery workers or silver jewelry workers with higher mean PbB (53.64 and 48.56 µg/dL, respectively), compared to controls (mean PbB: 12.52 µg/dL). Similarly, AST was elevated in painters with a mean PbB of 5.4 µg/dL, but no change in AST was

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Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects ^{b,c}
Al-Neamy et al. 2001	Mean (SD)	LFTs	<ul style="list-style-type: none"> • Greater: LDH, AP • No difference: ALT, AST, GGT, bilirubin, albumin
Cross-sectional study; n=100 workers; 100 controls	<ul style="list-style-type: none"> • Workers: 77.5 (42.8) • Controls: 19.8 (12.3) 		
Can et al. 2008	Mean (SD)	LFTs	Battery workers: <ul style="list-style-type: none"> • Greater LDH, AP, TC Muffler workers: <ul style="list-style-type: none"> • Greater^a LDH, AP
Cross-sectional study; n=22 battery workers; 38 muffler repair workers; 24 controls	<ul style="list-style-type: none"> • Battery workers: 36.83 (8.13) • Muffler workers: 26.99 (9.42) • Controls: 14.81 (3.01) 		
Chen et al. 2019	Median (P ₂₅ , P ₇₅)	LFTs	<ul style="list-style-type: none"> • Greater: GGT • No difference: AST, ALT, LDH
Cross-sectional study; n=158 exposed adults living near an electronic waste area; 109 controls	<ul style="list-style-type: none"> • Control: 5.1 (3.9, 8.4) • Exposed: 8.7 (6.2–12.2) 		
Conterato et al. 2013	Mean (SE)	LFTs	Painters: <ul style="list-style-type: none"> • Greater: AST • No difference: GGT Battery workers: <ul style="list-style-type: none"> • No difference: AST, GGT
Cross-sectional study; n=50 painters; 23 battery workers; and 36 controls	<ul style="list-style-type: none"> • Painters: 5.4 (0.4) • Battery workers 49.8 (4.0) • Controls: 1.5 (0.1) 		
Hsiao et al. 2001	Baseline: 60 Follow-up: 30	LFTs	No correlation of PbB to ALT
Longitudinal study (baseline 1989; follow-up 1999); n=30 battery workers			

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Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects ^{b,c}
Kasperczyk et al. 2013	Mean (SD); range	Liver size	<ul style="list-style-type: none"> Low PbB: Greater High PbB: Greater
Cross-sectional study; n (from Pb-Zn processing facility): 57 low Pb exposure; 88 high Pb exposure; and 36 controls	<ul style="list-style-type: none"> Low Pb: 28.66 (6.60); 20–35 High Pb: 40.58 (6.74); 35–60 Control: 8.34 (2.91) 	Gall bladder wall thickness	<ul style="list-style-type: none"> Low PbB: Greater High PbB: Greater
		LFTs	<ul style="list-style-type: none"> Low PbB: <ul style="list-style-type: none"> No difference: ALT, AST, LDH, GGT, bilirubin High PbB: <ul style="list-style-type: none"> No difference: ALT, LDH, AST, bilirubin Greater AST, GGT
Khan et al. 2008	Median (range)	LFTs	<ul style="list-style-type: none"> Greater ALT, GGT, albumin No change: AP, bilirubin
Cross-sectional study; n=87 workers; 61 controls	<ul style="list-style-type: none"> Workers: 29.1 (9.0–61.1) Controls: 8.3 (1.0–21.7) 		
Kristal-Boneh et al. 1999	Mean (SD)	Cholesterol and lipoproteins	<ul style="list-style-type: none"> Greater: TC, HDL No change: LDL, TG, HDL:TC ratio
Cross-sectional study; n=56 exposed; 87 controls	<ul style="list-style-type: none"> Workers: 42.3 (14.9) Controls: 2.7 (3.6) 		
Patil et al. 2007	Mean (SD)	LFTs	Battery workers:
Cross-sectional study; n=30 battery workers; 30 silver jewelry workers; 30 spray painters ^a ; 35 controls	<ul style="list-style-type: none"> Battery workers: 53.63 (16.98) Silver jewelry workers: 48.56 (7.39) Spray painters: 22.32 (8.87) Controls: 12.52 (4.08) 		<ul style="list-style-type: none"> Greater percentage change: albumin, bilirubin No change: ALT, AST Silver jewelry workers: <ul style="list-style-type: none"> Lesser percentage change: albumin compared to controls No change: ALT, AST, bilirubin compared to controls Spray painters: <ul style="list-style-type: none"> Greater percentage change: ALT, AST Decreased percentage change: albumin No change: bilirubin

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Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects ^{b,c}
Zhai et al. 2017	Quartiles (Q)	Non-alcoholic fatty liver disease	Men ^d : no association were observed for any PbB quartile
Cross-sectional study; n=214 men and 610 women with non-alcoholic fatty liver disease	Men: <ul style="list-style-type: none">• Q1: ≤3.60• Q2: 3.61–5.29• Q3: 5.30–7.28• Q4: ≥7.29		Women ^d : positive association between PbB at the two highest quartiles; OR (95% CI) <ul style="list-style-type: none">○ Q3: 1.495 (1.024, 2.181)*○ Q4: 1.613 (1.082, 2.405)*○ p for trend: 0.019
	Women: <ul style="list-style-type: none">• Q1: ≤2.97• Q2: 2.98–4.49• Q3: 4.50–6.59• Q4: ≥6.60		

^aReporting inconsistencies regarding number of spray painters evaluated; reported as 30 and 35.

^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

^cUnless otherwise specified, comparisons are to control groups.

^dComparison to lowest PbB quartile.

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CI = confidence interval; GGT = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LFT = liver function test (plasma activity of hepatic enzymes); Pb = lead; Q = quartiles; SD = standard deviation; SE = standard error; TC = total cholesterol; TG = triglycerides; Zn = zinc

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Table 2-20. Effects on Liver Function Tests Associated with Chronic Exposure to Lead (Pb)^a

Mean PbB (µg/dL)	Population (n) ^b	ALT	AST	GGT	LDH	AP	Reference
5.4	P (50)	–	↑	0	–	–	Conterato et al. 2013
8.7	G (158)	0	0	↑	0	↑	Chen et al. 2019
22.32	P (35) ^c	↑	↑	–	–	–	Patil et al. 2007
26.99	Pb-A (38)	0	0	0	↑	↑	Can et al. 2008
28.66	Pb-Zn (57)	0	0	0	0	0	Kasperczyk et al. 2013
29.1	Pb (87)	↑	–	↑	–	0	Khan et al. 2008
30	B (30)	0	–	–	–	–	Hsiao et al. 2001
36.83	B (22)	0	0	0	↑	0	Can et al. 2008
40.58	Pb-Zn (88)	0	↑	↑	0	↑	Kasperczyk et al. 2013
48.56	J (30)	0	0	–	–	–	Patil et al. 2007
9.8	B (23)	0	0	0	–	–	Conterato et al. 2013
53.63	B (30)	0	0	–	–	–	Patil et al. 2007
77.5	Pb (100)	0	0	0	↑	↑	Al-Neamy et al. 2001

^aReporting inconsistencies regarding number of spray painters evaluated; reported as 30 and 35.

↑ = increased; 0 = no change; – = not assessed; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; B = battery workers; G = general population; GGT = gamma-glutamyl transpeptidase; J = silver jewelry workers; LDH = lactate dehydrogenase; MDA = malondialdehyde; P = painters; Pb = Pb-exposed industrial workers; Pb-A = Pb-exposed auto workers; Pb-Zn = Pb-zinc processors

observed in battery workers with a mean PbB of 49.8 µg/dL, compared to controls with a mean PbB of 1.5 µg/dL (Conterato et al. 2013). Effects in painters with lower PbB compared to other workers with higher PbB may be due to co-exposure to other occupational chemicals. In a cross-sectional study of residents living close to an electronic waste site in China, PbB (median PbB: 8.7 µg/dL) was associated with an increase in gamma-glutamyl transpeptidase (GGT) compared to controls (median PbB: 5.1 µg/dL), although no effects were observed for ALT or AST (Chen et al. 2019). In addition to liver enzymes, total serum cholesterol and high-density lipoprotein (HDL)-cholesterol were greater in workers with a mean PbB of 26.99–42.3 µg/dL, compared to controls with a mean PbB 2.7–14.81 µg/dL (Can et al. 2008; Kristal-Boneh et al. 1999).

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Conterato et al. (2013), Chen et al. (2019), and Zhai et al. (2017).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of hepatic toxicity. EPA (2014c) specifically noted that oxidative stress

through ROS can result in damaged function and histopathological damage to the liver, including peroxidation of lipid membranes.

2.11 RENAL

Overview. Numerous epidemiologic studies in adults show that exposure to Pb can cause altered kidney function and contribute to the development of chronic kidney disease (CKD). A few studies in children also show decreases in renal function. Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive Pb exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed GFR. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979). Studies show consistent evidence of renal damage and reduced renal function associated over a wide range of PbB (≤ 10 – >50 $\mu\text{g/dL}$), with the overall dose-effect pattern suggesting an increasing severity of nephrotoxicity associated with increasing PbB.

The following renal effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Decreased GFR; corroborated in numerous studies.
 - Proteinuria; demonstrated in a few studies.
 - Chronic kidney disease (CKD); demonstrated in two studies.
- >10 $\mu\text{g/dL}$:
 - Decreased GFR; corroborated in numerous studies.
 - Enzymuria; corroborated in numerous studies.
 - Proteinuria; corroborated in numerous studies.
 - Impaired tubular transport; demonstrated in a few studies.
 - Histopathological damage; demonstrated in a few studies.

Measures of Effect. Endpoints demonstrating renal damage include various measures of glomerular and tubular dysfunction. Effects on GFR typically are assessed from measurements of creatinine clearance, serum creatinine concentration, or blood urea nitrogen (BUN). Increased excretion of albumin

(albuminuria) is an indication of damage to the glomerular endothelium or basement membrane, resulting in increased filtration of albumin, or impaired function of the proximal tubule, resulting in decreased reabsorption of filtered albumin. Increased excretion of low molecular weight serum proteins (e.g., 2 μ G or retinol-binding protein) are an indication of impaired reabsorption of protein in the proximal tubule. Increased excretion of enzymes associated with the renal tubule (renal tubular enzymuria) is an indication of injury to renal tubular cells resulting in release of membrane or intracellular enzymes into the tubular fluid. Pb-induced renal tubular enzymuria is most commonly evaluated from measurements of urinary N-acetyl-D-glucosaminidase (NAG). Increased excretion of NAG has been found in Pb-exposed workers in the absence of increased excretion of other proximal tubule enzymes (e.g., alanine aminopeptidase, alkaline phosphatase, glutamyltransferase) (Pergande et al. 1994). Indices of impaired transport include altered clearance or transport maxima for organic anions (e.g., p-aminohippurate, urate) or glucose (Biagini et al. 1977; Hong et al. 1980; Wedeen et al. 1975). Proximal tubular injury can also be confirmed through histopathological examination of renal tissue, although few studies provide this information (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979).

Measures of Exposure. Most studies evaluating renal damage use PbB as the biomarker for exposure, although more recent epidemiological studies have explored associations between toxicity and bone Pb concentrations. These studies provide a basis for establishing PbB, and, in some cases, bone Pb concentration ranges associated with specific nephrotoxicity outcomes.

Confounding Factors and Effect Modifiers. Inconsistencies in the reported outcomes for renal effects across studies may derive from several causes, including failure to account for confounding factors and effect modifiers. Various factors can affect kidney function, including age, underlying diseases (e.g., hypertension), and concomitant exposure to other nephrotoxics (e.g., cadmium). Results of epidemiological studies of general populations have shown an effect of age on the relationship between GFR (assessed from creatinine clearance of serum creatinine concentration or cystatin C) and PbB (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992). Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality) (Bellinger 2011; Diamond et al. 2019; Evans and Elinder 2011; Marsden 2003). Thus, reverse causality potentially confounds interpretation of the dose-response relationship between PbB and decreased renal function. Pb exposure has also been associated with increases in GFR (Hsiao et al. 2001; Roels et al. 1994). This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Hypertension can be both a confounder in studies of associations between Pb exposure and creatinine clearance (Perneger et al. 1993) and a covariable with Pb

exposure (Harlan et al. 1985; Muntner et al. 2003; Payton et al. 1994; Pirkle et al. 1985; Pocock et al. 1984, 1988; Tsaih et al. 2004; Weiss et al. 1986). Renal damage can cause increased blood pressure, which in turn can result in further damage to the kidneys. In addition, varying uncertainty also exists across studies in exposure history of subjects and in the biomarkers assessed.

Characterization of Effects. A large number of studies showing decrements in renal function associated with Pb exposure in humans have been published (Table 2-21). Most of these studies are of adults whose exposures were of occupational origin; however, a few environmental, mixed, and/or unknown exposures are represented, and a few studies of children are also included. Although these studies demonstrate adverse renal effects across the PbB range, some studies did not find associations (Buchet et al. 1980; de Kort et al. 1987; Fadrowski et al. 2010; Gennart et al. 1992; Huang et al. 2002; Karimooy et al. 2010; Mujaj et al. 2019; Omae et al. 1990). However, collectively, the body of evidence demonstrates that long-term exposure to Pb is nephrotoxic. General trends regarding the relationship between PbB and qualitative aspects of the kidney response are shown in Table 2-21. Decreased GFR and proteinuria have been observed in association with PbB ≤ 10 $\mu\text{g/dL}$; the significance of these studies is discussed in greater detail below. Enzymuria and proteinuria have been observed in association with PbB >10 – ≤ 50 $\mu\text{g/dL}$. Functional deficits, including enzymuria, proteinuria, impaired transport, and depressed GFR have been observed at PbB >50 $\mu\text{g/dL}$. Histopathological findings, including tubular atrophy, focal sclerosis of glomeruli, and periglomerular and interstitial fibrosis have also been observed at PbB >50 $\mu\text{g/dL}$. The overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs <10 $\mu\text{g/dL}$, enzymuria and proteinuria becoming evident >10 $\mu\text{g/dL}$, and severe deficits in function and pathological changes occurring in association with PbBs >50 $\mu\text{g/dL}$.

Table 2-21. Overview of Renal Effect Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) ($\mu\text{g/dL}$)	Effects associated with Pb exposure	References
≤ 10	Increased GFR	de Burbure et al. 2006
	Decreased GFR	Åkesson et al. 2005; Fadrowski et al. 2010; Harari et al. 2018; Lin et al. 2001; Khan et al. 2010a; Kim et al. 1996a; Lin et al. 2003; Lin et al. 2006a, 2006b; Muntner et al. 2003; Navas-Acien et al. 2009; Payton et al. 1994; Pollack et al. 2015; Spector et al. 2011; Staessen et al. 1992, 2001; Yu et al. 2004

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Table 2-21. Overview of Renal Effect Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Proteinuria chronic kidney disease	Navas-Acien et al. 2009; Harari et al. 2018; Pollack et al. 2015
>10–≤30	Decreased GFR	Kim et al. 1996a; Staessen et al. 1990
	Enzymuria	Bernard et al. 1995; Chia et al. 1994; Sonmez et al. 2002; Sun et al. 2008b
	Proteinuria	Bernard et al. 1995; Chia et al. 1995a, 1995b
>30–≤50	Increased GFR	Hsiao et al. 2001; Roels et al. 1994
	Decreased GFR	Orisakwe et al. 2007; Weaver et al. 2003a, 2003b, 2005a; Wedeen et al. 1975
	Enzymuria	Cardenas et al. 1993; Cardozo dos Santos et al. 1994; Fels et al. 1994; Garcon et al. 2007; Gerhardsson et al. 1992; Kim et al. 1996a; Kumar and Krishnaswamy 1995; Lin and Tai-yi 2007; Mortada et al. 2001; Pergande et al. 1994; Roels et al. 1994; Verberk et al. 1996; Verschoor et al. 1987; Weaver et al. 2003a, 2003b, 2005a
	Proteinuria	Factor-Litvak et al. 1999; Fels et al. 1998; Garcon et al. 2007; Gerhardsson et al. 1992; Kumar and Krishnaswamy 1995; Mortada et al. 2001; Pergande et al. 1994; Verschoor et al. 1987
	Impaired tubular transport	Pinto de Almeida et al. 1987
>50	Decreased GFR	Baker et al. 1979; Biagini et al. 1977; Cramer et al. 1974; Ehrlich et al. 1998; Hong et al. 1980; Lilis et al. 1968, 1980; Onuegbu et al. 2011; Wedeen et al. 1975, 1979
	Enzymuria	Cabral et al. 2012; Gao et al. 2010; Garcon et al. 2007
	Proteinuria	Cabral et al. 2012; Gao et al. 2010; Garcon et al. 2007
	Impaired tubular transport	Biagini et al. 1977; Ehrlich et al. 1998; Hong et al. 1980; Wedeen et al. 1975
	Histopathological changes	Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979

GFR = glomerular filtration rate

Effects at Blood Pb Levels ≤10 µg/dL. Studies of renal function in populations with PbB ≤10 µg/dL provide evidence for effects of Pb on GFR in children and adults. Results are summarized in Table 2-22, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 6. Most studies found that increasing PbB was associated with decreased GFR; however, one study found evidence for increasing GFR in children (de Burbure et al. 2006).

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated ^c	Result ^d
Akesson et al. 2005	Median: 2.2	CCr	Linear regression β coefficient (mL/minute per $\mu\text{g/dL}$): -0.018 (95% CI -0.03, -0.006)*
Cross-sectional study; n=820 adult women		GFR	Linear regression β coefficient (mL/minute per $\mu\text{g/dL}$): -0.02 (95% CI -0.03, -0.009)*
		UPHC	Linear regression β coefficient ($\mu\text{g/L}$ per $\mu\text{g/dL}$): reported as NS
		UNAG	Linear regression β coefficient (U/g creatinine per $\mu\text{g/dL}$): reported as NS
Barry et al. 2019	Median: 2.5	GFR	Linear regression coefficient (SE) for: PbB Q4: -2.71 (4.16); p=0.52 PbB continuous: -0.13 (0.28); p=0.65 Bone Pb Q4: -5.66 (4.86); p=0.25 Bone Pb Continuous: -0.15 (0.11); p=0.18
Cross-sectional study; n=211 adult men			
de Burbure et al. 2006	Mean range (three locations) Control: 2.81–3.81 Exposure: 3.64–6.51	SCr	Decreased 7% (p<0.01) in Q4 (PbB >5.59 $\mu\text{g/dL}$), compared to Q1 (PbB <2.85 $\mu\text{g/dL}$)*
Cross-sectional study; n>800 children (ages 8.5–12.3 years)		Sp2M	Decreased 9% (p<0.01) in Q4 (PbB >5.86 $\mu\text{g/dL}$), compared to Q1 (PbB <3.10 $\mu\text{g/dL}$)*
Fadrowski et al. 2010	Median: 1.5 Quartiles: • Q1: <1.0 • Q2: 1.0–1.5 • Q3: 1.6–2.9 • Q4: >2.9	GFR	<ul style="list-style-type: none"> Change in GFR (mL/minute/1.73 m²) Q4 compared to Q1: -6.6 (-12.6, -0.7)* p-Trend across Q1–Q4=0.009* Mean difference in GFR associated with a 2-fold increase in blood lead level: -2.9 (-5.0, -0.7)*
Cross-sectional study; n=769 adolescents (ages 12–20 years)			

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated ^c	Result ^d
Harari et al. 2018 Prospective cohort study; n=2,567 adults; with a 16-year follow-up period	Median at baseline (range): GFR 2.5 (0.15–25.8) Quartiles (range): • Q1: 1.5 (0.15–1.85) • Q2: 2.2 (1.85–2.47) • Q3: 2.9 (2.47–3.30) • Q4: 4.6 (3.30–25.8)	At follow-up, GFR for Q1 decreased from 89 to 62 mL/minute from baseline Additional decreases in GFR, mL/minute/1.73 m², per quartile: • Q3: -2.6 (-4.0, -1.2); p<0.001* • Q4: -2.3 (-3.8, -0.85); p=0.002* • p-trend: <0.001*	
Kim et al. 1996a Retrospective cohort study; n=459 men	Mean: 9.9	CKD	HR for Q4 compared to combined Q1–Q3: 1.49 (1.07–2.08); p=0.02* • Regression coefficient (SE) for all participants ($\mu\text{mol/L}$ per $\mu\text{g/dL}$): 0.033 (0.012); p=0.005* • Regression coefficient (SE) for PbB ≤ 10 ($\mu\text{mol/L}$ per $\mu\text{g/dL}$): 0.060 (0.019); p=0.002*
Khan et al. 2010 Cross sectional study children (ages 1–6 years) of Pb workers (n=123) and controls (n=123)	Median • Control: 6.7 • Exposed: 8.10	SCr	• Serum creatinine ($\mu\text{mol/L}$): control: 52; exposed: 56; p ≤ 0.01 * • Spearman's correlation coefficient: r=0.13; p ≤ 0.05 *
Lin et al. 2001 Prospective, longitudinal study; n=110 patients with chronic renal insufficiency	Low PbB mean: 3.9 High PbB mean: 6.6	CCr	• 18 Months CCr (mL/second) mean \pm SD: low Pb: 0.72 \pm 0.25; high Pb: 0.59 \pm 0.22 $\mu\text{g/dL}$ (p=0.007)* • 21 Months CCr (mL/second) mean \pm SD: low Pb: 0.70 \pm 0.24; High Pb: 0.57 \pm 0.22 $\mu\text{g/dL}$ (p=0.006)* • 24 Months CCr (mL/second) mean \pm SD: low Pb: 0.70 \pm 0.24; High Pb: 0.55 \pm 0.22 $\mu\text{g/dL}$ (p=0.001)*

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated ^c	Result ^d
Lin et al. 2003 Prospective, longitudinal study; n=202 patients with chronic renal insufficiency	Baseline: 5.3 After 24-month observation, prior to chelation ^e • Placebo: 5.9 • Chelation: 6.1	GFR	<ul style="list-style-type: none"> GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo 25.5 ± 12.3; chelation 34.4 ± 14.7 ($p=0.01$)* Change in GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo -6.0 ± 5.8; chelation 2.1 ± 5.7 ($p>0.001$)*
Lin et al. 2006a Prospective, longitudinal study; n=124 patients with chronic renal insufficiency	After 24-month observation, prior to chelation ^e • Placebo: 3.0 • Chelation: 2.6	GFR	<ul style="list-style-type: none"> GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo 38.0 ± 8.9; chelation 47.9 ± 17.0 ($p=0.0493$)* Change in GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo -4.6 ± 4.3; chelation 6.6 ± 10.7 ($p>0.0005$)*
		UP (24-hour)	<ul style="list-style-type: none"> Urine protein (g) following chelation: placebo 1.11 ± 1.63; chelation: 0.92 ± 1.16 ($p=0.6236$)
Lin et al. 2006b Prospective, longitudinal study; n=238 patients with type II diabetes and progressive diabetic neuropathy	End of 12-month observation, prior to chelation ^e • Placebo: 5.9 • Chelation: 7.5	GFR	<ul style="list-style-type: none"> GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo 13.1 ± 4.5; chelation 18.0 ± 7.3 ($p=0.0352$)* Decrements in GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo 13.2 ± 7.6; chelation 4.4 ± 6.8 ($p>0.0045$)*
Lin-Tan et al. 2007 Placebo-controlled clinical study; n=116 non-diabetic patients with chronic kidney disease	Mean after 51-month chelation • Placebo: 6.0 • Chelation: 3.5	GFR	<ul style="list-style-type: none"> GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo 23.7 ± 10.8; Chelation 35.4 ± 17.0 ($p<0.0001$)* Change in GFR ($\text{mL}/\text{minute}/1.73 \text{ m}^2$) following treatment ($\text{mean} \pm \text{SD}$): placebo -12.7 ± 8.4; chelation -1.8 ± 8.8 ($p>0.0001$)*
		UP (24-hour)	UP ($\text{mean} \pm \text{SD}$): placebo 0.96 ± 1.04 ; chelation: 0.81 ± 0.86 ($p=0.3369$)

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated ^c	Result ^d
Mujaj et al. 2019	Mean: 4.34	GFR	β , per doubling of PbB: -0.281 (-3.07, 2.50); p=0.84
Cross-sectional study; n=447 newly hired male workers		ACR	β , per doubling of PbB: -0.071 (-0.14, 0.59); p=0.06
Muntner et al. 2003	Normotensive Mean: 3.30 \pm 0.10 Quartiles: • Q1 (reference): 0.7–1.6 • Q2: 1.7–2.8 • Q3: 2.9–4.6 • Q4: 4.7–52.9 Hypertensive Mean: 4.21 \pm 0.14 Quartiles: • Q1 (reference): 0.7–2.4 • Q2: 2.5–3.8 • Q3: 3.9–5.9 • Q4: 6.0–56.0	GFR	Estimated GFR, mL/minute (mean \pm SD) • Normotensive: 115 \pm 0.7 • Hypertensive: 95 \pm 0.7 (p<0.001)*
Cross-sectional study; n=4,813 hypertensive; n=10,398 normotensive adults ^g		SCr	OR for elevated SCr in hypertensive patients: Q2: 1.47 (1.03, 2.10)* Q3: 1.80 (1.34, 2.42)* Q4: 2.41 (1.46, 3.97)* p-trend: <0.001*
		CKD	OR for elevated CKD in hypertensive patients: Q2: 1.44 (1.00, 2.09) Q3: 1.85 (1.32, 2.59)* Q4: 2.60 (1.52, 4.45)* p-trend: <0.001*
Navas-Acien et al. 2009^f	Mean: 1.58 Quartiles: • Q1 (reference): ≤ 1.1 • Q2: >1.1–1.6 • Q3: >1.6–2.4 • Q4: >2.4	GFR	ORs for reduced GFR • Q2: 1.10 (0.80, 1.51) • Q3: 1.36 (0.99, 1.85) • Q4: 1.56 (1.17, 2.08)* • p-trend: <0.001*
Cross-sectional study; n=14,778 adults		Albuminuria	ORs for albuminuria • Q2: 0.83 (0.66, 1.04) • Q3: 0.92 (0.76, 1.12) • Q4: 1.19 (0.96, 1.47) • p-trend: <0.001*

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated ^c	Result ^d
Payton et al. 1994	Mean: 8.1	CCr	Regression coefficient, β (SE), mL/minute per $\mu\text{g}/\text{dL}$: -0.0403 (0.0198); $p=0.0426^*$
Cross-sectional study; n=744 men			
Pollack et al. 2015	Median: 0.88 Tertiles:	GFR	<ul style="list-style-type: none"> Regression β coefficient (% change per twofold increase in PbB): -3.73 (-6.55, -0.83)[*] Regression β coefficient (% change per 2-fold increase in PbB) by tertile: <ul style="list-style-type: none"> T2: -8.28 (-14.07, -2.5); $p<0.05^*$ T3: -6.79 (-13.10, -0.49); $p<0.05^*$
Prospective cohort study; n=257 premenopausal women	<ul style="list-style-type: none"> T1 (reference): <0.72 T2: 0.72–1.10 T3: >1.10 		
		SCr	Regression β coefficient (% change per 2-fold increase in PbB): 3.47 (0.86, 6.16)
		BUN	Regression β coefficient (% change per 2-fold increase in PbB): -0.13 (-4.97, 4.96)
		Blood albumin	Regression β coefficient (% change per 2-fold increase in PbB): -0.38 (-1.28, 0.52)
		Blood glucose	Regression β coefficient (% change per 2-fold increase in PbB): 0.93 (-0.28, 2.15)
		Blood protein	Regression β coefficient (% change per 2-fold increase in PbB): -0.76 (-1.61, 0.09)

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated ^c	Result ^d
Spector et al. 2011^f Cross-sectional study; n=3,941 adults	Mean (all): 1.7 Mean (≥ 60 years) Tertiles (all): • T1 (reference): ≤ 1.3 • T2: $> 1.3-2.2$ • T3: > 2.2	GFR	<ul style="list-style-type: none"> All participants: change in GFR (mL/minute/1.73 m²) per 2-fold increase in PbB: -1.9 (-3.2, -0.7)* All participants: OR for reduced GFR by tertiles <ul style="list-style-type: none"> T2: -1.6 (-4.2, 1.0) T3: -3.3 (-5.3, -1.4)* p-trend: 0.001* Participants ≥ 60 years: change in GFR (mL/minute/1.73 m²) per 2-fold increase in PbB: -4.5 (-5.6, -3.3)
Staessen et al. 1992 Cross-sectional study; n=1,981 adults (965 men; 1,016 women)	Mean men: 11.4 Mean women: 7.5	CCr	Partial regression coefficient (SE) for CCr (mL/minute per log $\mu\text{g Pb/L}$): <ul style="list-style-type: none"> Men: -13.1 (4.0); $p \leq 0.001$* Women: -30.1 (3.4); $p \leq 0.001$*
Staessen et al. 2001 Cross-sectional study; n=200 17-year-old adolescent girls	Mean control: 1.4 Mean exposed area 1: 1.8 Mean exposed area 2: 2.7	Serum cystatin C Urine β_2 -microglobulin	Change in per 2-fold increase in PbB: +3.6% (1.5, 5.7)* Change per 2-fold increase in PbB: +16.0% (2.7, 31)*
Tsaih et al. 2004 Prospective study; n=448 (66–72 years of age); n=26 participants with diabetes, and n=115 participants with hypertension	Mean at baseline: 6.5 Mean at follow-up: 4.5	SCr	Baseline regression β coefficients (mg/dL per ln $\mu\text{g/dL}$): <ul style="list-style-type: none"> All participants: 0.009 (SE 0.006) Participants with diabetes: 0.076 (SE 0.023); $p < 0.05$* Participants with hypertension: 0.008 (0.010); Follow-up (4–8 years) regression β coefficients (mg/dL per ln $\mu\text{g/dL}$): <ul style="list-style-type: none"> Participants with diabetes: 0.223 (SE 0.183); Participants with hypertension: 0.352 (0.097); $p < 0.05$*

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Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated ^c	Result ^d
Yu et al. 2004	Mean: 4.2	GFR	Change in GFR ($\text{mL/minute/1.73 m}^2$ per 1 $\mu\text{g/dL}$): -4.0 ($p=0.0148$) ^e
Prospective longitudinal study; n=121 patients with chronic renal insufficiency; progression of renal insufficiency was evaluated for 48 months			

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 6 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.

^cA variety of methods are used to estimate GFR (Chao et al. 2015). Each has limitations for application to both clinical evaluations and epidemiology. The preferred method is to measure the clearance of substance from plasma that is known to be eliminated solely by glomerular filtration and is not reabsorbed in the renal tubule. Typically, in the clinical setting, this is accomplished with intravenous administration of GFR markers, such as ^{125}I -iothalamate, for the radiocontrast agent (e.g., iohexol). These procedures are feasible in the clinical setting, but not in epidemiology studies in which invasive procedures and administration of such agents is not practical or possible. Clearance of endogenous creatinine is an alternative that has had wide use in epidemiology. However, it requires concurrent measurements of serum creatinine and the rate of urinary excretion of creatinine, which can be accurately determined only with a carefully timed urine sample that can represent the amount of glomerular filtrate formed over a given time interval. Achieving accurately timed urine samples requires a rigidly implemented and supervised collection protocol, which is not always feasible, particularly in large-scale epidemiology studies. Alternatives to clearance methods are measurement of endogenous metabolites in plasma whose clearance approximates GFR. Typically, this is achieved with endogenous creatinine or cystatin C. The serum concentration of these two metabolites strongly correlates with GFR; however, the relationship between concentration and GFR is also affected by other variables, including age, sex, race, and creatinine muscle mass. Several approaches have been developed to improve estimates of GFR from serum creatinine that attempt to account for these co-variables. These methods rely on multiple variable regression models that relate GFR to serum creatinine and other significant determinants of GFR (Cockcroft and Gault 1976; Levey et al. 1999, 2009). An evaluation of two of the more commonly used methods for estimating GFR from serum creatinine, the CKD-EPI and MDRD equations, found that both achieved a median difference between calculated and measured GFR (from clearance measurements) that range from 2 to 6 $\text{mL/minute per 1.73 m}^2$ (Levey et al. 2009). The interquartile range in the difference was approximately 18 $\text{mL/minute per 1.73 m}^2$ in a validation dataset consisting of data for 3,986 study subjects. This suggests that approximately 25% of the GFR estimates from these methods are expected to be in error of the true GFR by >18 mL/minute (or approximately 15% of the GFR in a healthy adult, 120 mL/minute).

^dAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

^eBlood lead estimated by EDTA mobilization.^fPopulation from NHANES.

ACR = albumin-to-creatinine ratio; BUN = blood urea nitrogen; CCr = creatinine clearance; CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; EDTA = ethylenediaminetetraacetic acid; GFR = glomerular filtration rate; HR = hazard ratio; MDRD = Modification of Diet in Renal Disease; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PbB = serum β_2 -microglobulin; SCr = serum creatinine concentration; SD = standard deviation; SE = standard error; UNAG = urine N-acetyl- β -D-glucosaminidase; UP = urine protein; UPHC = urine human complex-forming protein (α_1 -microglobulin)

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A few studies have examined associations between low PbB and GFR in children and adolescents (de Burbure et al. 2006; Fadrowski et al. 2010; Khan et al. 2010a; Staessen et al. 2001). de Burbure et al. (2006) examined serum creatinine in a cross-sectional study of approximately 800 children (age range 8.5–12.3 years) who resided near nonferrous smelters. Serum creatinine and cystatin C decreased (indicating an increase in GFR) by approximately 7% in the upper quartile PbB group (mean 7.8 µg/dL) compared to the lowest quartile (<2.84 µg/dL). Fadrowski et al. (2010) examined adolescents (12–20 years, n=769). GFR (estimated from serum cystatin C) decreased with increasing PbB. In the upper quartile PbB group (>2.9 µg/dL), the decrease was 6.6 mL/minute/1.73 m², which represented approximately a 6% decrease in GFR. In a smaller study of younger children of Pb-exposed workers (ages 1–6 years; n=123; PbB: 8.1 µg/dL), serum creatinine was higher compared to controls (ages 1–6 years; n=123; PbB: 6.7 µg/dL) (Khan et al. 2010), indicating decreased GFR. Several factors may have contributed to the different outcomes in these studies (decrease or increase in GFR), including a different age range of the study groups, different approaches to adjusting outcome metrics for confounders, and different exposures (e.g., co-exposure to Pb, cadmium, and mercury in the de Burbure et al. 2006 study).

A smaller study of adolescents (17 years of age, n=200) also found evidence for higher serum cystatin C (indicating lower GFR) in a group with a mean PbB of 2.7 µg/dL compared to a group with a mean PbB of 1.4 µg/dL (Staessen et al. 2001).

A larger number of studies have been conducted in adult populations (Table 2-22). These include several prospective studies (Harari et al. 2018; Lin et al. 2001, 2003, 2006a, 2006b; Lin-Tan et al. 2007; Pollack et al. 2015; Tsaih et al. 2004; Yu et al. 2004). Most of these studies have examined changes in GFR in patients who had ongoing renal disease and depressed GFR (Lin et al. 2001, 2003, 2006a, 2006b; Lin-Tan et al. 2007; Yu et al. 2004). In adult participants with a median baseline PbB of 2.5 µg/dL, GFR decreased from 89 to 62 mL/minute after 16 years; GFR further decreased with increasing PbB (Harari et al. 2018). In addition, the risk of CKD was increased in participants with a median PbB of 4.6 µg/dL compared to participants with a PbB range of 0.15–3.30 µg/dL. In adult patients who had indications of renal insufficiency (e.g., serum creatinine concentration >1.5 mg/dL), GFR increased following repeated chelation therapy with calcium disodium ethylenediaminetetraacetic acid (EDTA) (Lin et al. 2003, 2006b). Yu et al. (2004) estimated the decline in GFR in patients with renal insufficiency to be approximately 4 mL/minute/1.73 m² per 1 µg/dL increase in PbB. A prospective study of premenopausal women estimated the decline in GFR to be approximately 3.73% per doubling of PbB (Pollack et al. 2015). The median PbB in the cohort was 0.88 µg/dL. A prospective study of older males found an association between increased serum creatinine (indicative in decreasing GFR) and PbB in subjects

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diagnosed with hypertension or diabetes. Mean PbBs were 6.5 µg/dL at baseline and 4.5 µg/dL at follow-up (Tsaih et al. 2004).

Several large cross-sectional studies have examined associations between PbB and GFR in adults (Table 2-22). Three large studies relied on data collected in the NHANES (Munter et al. 2003; Navas-Acien et al. 2009; Spector et al. 2011). The Munter et al. (2003) study, which included 4,813 hypertensive subjects and 10,938 normotensive subjects, found an association between increasing PbB and decreasing GFR in the hypertensive group. Navas-Acien et al. (2009) included 14,788 adult subjects and reported decreased GFR (<60 mL/minute/1.73 m²) among participants in the highest PbB quartile (mean >2.4 µg/dL). Spector et al. (2011) included 3,941 adults. In the age group ≥60 years, the estimate for the decline in GFR was 4.5 mL/minute/1.73 m² per doubling of PbB. The mean PbB in this group was 2.2 µg/dL. Several smaller cross-sectional studies have also found associations between increasing PbB and decreasing GFR in adult populations in which mean or median PbBs were <10 µg/dL (Åkesson et al. 2005; Payton et al. 1994; Staessen et al. 1992). Collectively, these studies indicate that Pb exposure is associated with decreasing GFR, and effects on GFR are evident in populations with PbB <10 µg/dL. People with on-going renal disease or hypertension may be more vulnerable to the effects of Pb. Estimates of the decline in GFR associated with increasing PbB vary across studies, with some studies indicating declines of 3–6 mL/minute/1.73 m² at PbB <10 µg/dL (Pollack et al. 2015; Spector et al. 2011; Yu et al. 2004). However, as noted above, the estimates may be inflated by reverse causality for associations between decreasing GFR and increasing Pb body burden.

Associations Between Bone Pb and Renal Effects. Studies evaluating associations between bone Pb and renal function are summarized in Table 2-23. Weaver et al. (2003a, 2005a, 2005b, 2006, 2009) conducted a series of studies evaluating associations between bone Pb and metrics of renal GFR (e.g., serum creatinine concentration, creatinine clearance calculated from serum creatinine concentration, BUN) and renal tubular injury (urinary NAG) in current and former Pb workers in South Korea. These studies provide evidence that tibia Pb is positively associated with serum creatinine concentration in older workers (Weaver et al. 2003a, 2005a, 2005b) and in male, but not female, workers (Weaver et al. 2009); and negatively associated with tibia Pb and creatinine clearance in male workers (Weaver et al. 2009) and in workers with vitamin D receptor (VDR) genotypes BB and Bb (Weaver et al. 2006). Tibia Pb was also positively associated with urinary NAG in older workers (Weaver et al. 2005a). Studies of participants of the longitudinal Normative Aging Study have found positive associations between tibia Pb and serum creatinine concentration in participants with diabetes (Tsaih et al. 2004) and with ALAD genotypes 1-2 and 2-2 (Wu et al. 2003a). One cross-sectional study did not find an association between tibia Pb and

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estimated GFR (Barry et al. 2019). A small case-control study did not find an association between tibia Pb and end-stage renal disease. Taken together, the results suggest that long-term exposure to Pb is associated with diminished renal function.

Table 2-23. Associations Between Bone Pb and Renal Function

Reference	Population	Effect						
		GFR	SCr	CCr	NAG	RBP	BUN	ESRD
Barry et al. 2019	211 adult men	0 (T)	–	–	–	–	–	–
Muntner et al. 2007	55 adult ESRD patients; 53 controls	–	–	–	–	–	–	0 T
Tsaih et al. 2004	448 men ^a	–	0 T ↑ T (diabetics) 0 P 0 P (diabetics)	–	–	–	–	–
Weaver et al. 2003a	803 adult Pb workers; 135 controls ^b	–	0 T (all workers) ↑ T (>46 years ^c)	0 T ^c	0 T ^c	0 T ^c	0 T ^c	–
Weaver et al. 2005a	803 adult Pb workers ^b	–	↑ T (>46 years ^c)	–	↑ T (>46 years) ^c	–	–	–
Weaver et al. 2005b	795 adult Pb workers ^b	–	↑ T (>40.6 years)	–	–	–	–	–
Weaver et al. 2006	647 adult Pb workers ^b	–	0 T (VDR ^d) 0 T (VDR ^e) 0 P (VDR ^d) 0 P (VDR ^e)	0 T (VDR ^d) ↓ T (VDR ^e) 0 P (VDR ^d) 0 P (VDR ^e)	–	–	–	–
Weaver et al. 2009	398 adult male and 139 female Pb workers ^b	–	↑ T (M) 0 T (F)	↓ T (M) 0 T (F)	–	–	0 T (M) ↑ T (F)	–

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Table 2-23. Associations Between Bone Pb and Renal Function

Reference	Population	Effect						
		GFR	SCr	CCr	NAG	RBP	BUN	ESRD
Wu et al. 2003a	709 men ^a	–	↑ T (ALAD ^f) 0 P	0 T ↓ P	–	–	–	–

^aParticipants in the Normative Aging Study.^bCurrent and former Pb workers in South Korea.^cData were analyzed for all study participants and by age tertiles (Tertile 1: ≤36 years old; Tertile 2: 36.1–46 years old; Tertile 3: >46 years old). Any association observed in a specific age tertile are noted. If no association was observed for all participants and for all age tertiles, this is noted with a single entry of 0.^dVitamin D receptor genotype bb.^eVitamin D receptor genotypes BB and Bb.^fInteraction between ALAD genotype (ALAD 1-2/2-2 versus ALAD 1-1).

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; ALAD = aminolevulinic acid dehydratase; BUN = blood urea nitrogen; CCr = creatinine clearance; ESRD = end-stage renal disease; F = female; M = male; NAG = N-acetyl-D-glucosaminidase; P = patella; Pb = lead; RBP = retinol binding protein; SCr = serum creatinine concentration; T = tibia; VDR = vitamin D receptor

Mechanisms of Action. Several mechanisms have been established or proposed as mechanisms for kidney damage associated with exposure to Pb, including general mechanisms of Pb-induced toxicity (reviewed in Section 2.21). Mechanisms of renal damage associated with Pb exposure were recently reviewed in detail by EPA (2014c), including oxidative stress, inflammation, apoptosis of glomerular and tubular cells, alterations in renal gangliosides (plasma membrane lipids that play a role in the control of GFR), changes in renal vascular tone, and alterations in the renin-angiotensin-aldosterone system. As discussed in Pb Section 3.1.2 (Toxicokinetics, Distribution), Pb is distributed to the kidney, providing a toxicokinetic mechanism for direct effects to the kidney.

2.12 DERMAL

No epidemiological studies evaluating adverse dermal effects of chronic exposure to Pb were identified.

2.13 OCULAR

Few epidemiological studies have evaluated non-neurological ocular effects of Pb exposure, with studies examining associations with macular degeneration (Erie et al. 2009; Park et al. 2015) and cataract development (Schaumberg et al. 2004). In a cross-sectional study of 3,865 participants with a mean PbB of 2.69 µg/dL participating in the Korea National Health and Nutrition Examination study (2008–2011),

the risks of age-related early (adjusted OR 1.12; 95% CI 1.02, 1.23; $p=0.009$) and late (adjusted OR 1.25; 95% CI 1.05, 1.50; $p=0.015$) macular degeneration were increased (Park et al. 2015). A cross-sectional study of human donor eyes with ($n=25$) and without ($n=36$) age-related macular degeneration found no association between Pb concentration in the retinal pigment epithelium-choroid complex and subjects with age-related macular degeneration and normal subjects (Erie et al. 2009). A prospective study of 642 men participating in the Normative Aging Study found no association between PbB (range: 1.0–35.0 $\mu\text{g/dL}$) and risk of cataracts, although the risk of cataracts was increased in association with tibia Pb levels (Schaumberg et al. 2004). A prospective cohort study of 634 male participants of the Normative Aging Study found an association between patellar bone Pb concentration and incidence of primary open-angle glaucoma, with an HR of 5.06 (95% CI 1.61, 15.88; $p=0.005$) (Wang et al. 2018).

2.14 ENDOCRINE

Effects of chronic exposure to Pb on reproductive hormones are reviewed in Section 2.17 (Reproductive).

Overview. Effects on endocrine systems have been evaluated in several epidemiological studies in adults (general populations and workers), adolescents, and children. Investigations have focused on effects on thyroid function, cortisol levels, vitamin D levels, serum levels of other growth factors, and diabetes. Associations between PbB and thyroid function, assessed by measurement of serum thyroid hormone levels, is the most investigated endocrine outcome, although results do not demonstrate a consistent pattern of effect or dose-response relationships. Other endocrine endpoints have been evaluated in only a few studies.

The following endocrine effects have been associated with PbB:

- $\leq 10 \mu\text{g/dL}$:
 - Altered serum levels of thyroid hormones (thyroxine [T4], triiodothyronine [T3], thyroid-stimulating hormone [TSH]); evaluated in multiple studies. Few effects were observed and results do not demonstrate consistent patterns of effects or exposure-response relationships.
 - Altered salivary cortisol awakening response in pregnant women.
 - Increased stress-induced salivary cortisol response in children.
 - Decreased serum levels of insulin-like growth factor-1 (IGF-1) in children.

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- >10 µg/dL:
 - Altered serum levels of thyroid hormones (T4, T3, TSH); evaluated in a few studies; results do not demonstrate consistent patterns of effects or exposure-response relationships.
 - Increased thyroid peroxidase antibodies.
 - Decreased serum levels of vitamin D; evaluated in a few studies in children with consistent results.

Measures of Exposure. Studies evaluating the association between endocrine effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Results of epidemiological studies on endocrine effects have not been consistent. In general, statistical analyses were not rigorous and potential confounding factors and effect modifiers were not fully considered. Exposure to other metals and other chemical with endocrine effects is an important confounding factor to consider when interpreting study results. Although a few studies were of large populations (e.g., NHANES participants); most studies examined relatively small populations and used cross-sectional designs.

Characterization of Effects. General trends for studies showing a relationship between PbB and endocrine effects are shown in Table 2-24. Several studies have evaluated associations between PbB and effects on serum levels of thyroid hormones (T4, T3, and TSH) at mean PbB ranging from <1 to 71 µg/dL; an overview of study results is presented in Table 2-25. Based on evaluation of thyroid hormones, it is unclear if PbB is associated with altered thyroid function. At PbB ≤10 µg/dL, results of epidemiological studies, including cross-sectional studies of large NHANES populations, show associations between PbB and some alterations in serum levels of thyroid hormones; however, results do not demonstrate apparent patterns or exposure response relationships (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*). Increased thyroid peroxidase (TPO) antibodies were observed at PbB ≤10 µg/dL, although TSH was not increased. Epidemiological studies at PbB >10 µg/dL, conducted in smaller populations (n=25–309), show more effects on thyroid hormones than observed at PbB ≤10 µg/dL. However, similar to studies at lower PbB, results are inconsistent. Kahn et al. (2014) found decreased T4 (p<0.0001) and increased TPO antibodies (p=0.0002) during the second trimester of pregnancy in women (n=144) with mean PbB 20.00 µg/dL compared to women (n=147) with PbB of 5.57 µg/dL; no increase in TSH was observed. The adjusted OR (95% CI) for testing positive for TPO antibodies was 2.41 (1.563, 3.82). Results indicate that autoimmunity is a potential mechanism for altered thyroid function. This finding has not been corroborated in other studies.

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Table 2-24. Overview of Endocrine Effects Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Altered levels of thyroid hormones ^a and increased TPO antibodies	Abdelouahab et al. 2008; Dundar et al. 2006; Luo and Hendryx 2014; Mendy et al. 2013; Nie et al. 2017; Yorita Christensen 2013
	Altered salivary cortisol levels	Braun et al. 2014; Gump et al. 2008
	Decreased serum IGF-1	Fleisch et al. 2013
>10–30	Altered levels of thyroid hormones ^a and increased TPO antibodies	Gustafson et al. 1989; Kahn et al. 2014; Lamb et al. 2008; Lopez et al. 2000
>30–50	Decreased serum vitamin D level	Luo and Hendryx 2014; Mahaffey et al. 1982; Rosen et al. 1980
>50	Altered levels of thyroid hormones ^a	Lopez et al. 2000; Pekcici et al. 2010; Robins et al. 1983; Singh et al. 2000; Tuppurainen et al. 1988
	Decreased serum vitamin D level	Rosen et al. 1980

^aThyroid hormones: T4, T3, and/or TSH.

IGF-1 = insulin-like growth factor-1; PbB = blood lead concentration; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TPO = thyroid peroxidase

Table 2-25. Effects on Thyroid Hormones Associated with Blood Lead Concentration (PbB)

Mean PbB (µg/dL)	Number of participants	T4		T3		TSH	Reference
		Total	Free	Total	Free		
PbB ≤10 µg/dL							
0.93	1,109 adolescents ^a	0	0	0	0	0	Chen et al. 2013
1.3	1,587 adults ^a	↓	0	0	0	0	Yorita Christensen 2013
1.52	4,652 adults ^a	↓	0	0	0	0	Mendy et al. 2013
1.74	87 women	0	–	0	–	↓	Abdelouahab et al. 2008
1.75	4,409 adults ^a	0	0	0	0	0	Chen et al. 2013
1.82	6,231 adults ^a	–	0	–	↑	0	Luo and Hendryx 2014
3.5	3,350 women	–	–	–	–	0	Nie et al. 2017
4.1	2,278 men	–	–	–	–	0	Nie et al. 2017
6.3 ^b	24 infants ^b	–	0	–	–	0	Iijama et al. 2007
7.3	42 adolescents	–	↓	–	0	0	Dundar et al. 2006
PbB >10 µg/dL							
20.00	291 adults	–	↓	–	–	0	Kahn et al. 2014
20.56	309 pregnancy ^c	–	↓	–	–	–	Lamb et al. 2008
24.1	151 adults	0	0	–	–	0	Schumacher et al. 1998
25	68 children	0	0	–	–	–	Siegel et al. 1989

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Table 2-25. Effects on Thyroid Hormones Associated with Blood Lead Concentration (PbB)

Mean PbB (µg/dL)	Number of participants	T4		T3		TSH	Reference
		Total	Free	Total	Free		
31	77 adults	–	0	–	0	0	Erfurth et al. 2001
<33.19 ^c	6,231 adults ^a	0	–	–	↑	0	Luo and Hendryx 2014
39.5	25 adults	↑	–	–	–	↑	Gustafson et al. 1989
50.9	75 adults	↑	↓	0	–	0	Lopez et al. 2000
51.9	47 adults	↓	↓	–	–	0	Robins et al. 1983
51.9	58 adults	0	–	↓	–	↑	Singh et al. 2000
56.1	176 adults	↓	↓	0	–	0	Tuppurainen et al. 1988
71.1	65 adults	–	↑	–	↑	↑	Pekcici et al. 2010

^aNHANES population.^bUmbilical cord PbB; assessments in infants.^cMean not reported.

↑ = Increased; ↓ = decreased; 0 = no change; – = not assessed; NHANES = National Health and Nutrition Examination Survey; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

Studies also have investigated alterations in serum levels of vitamin D at PbB >30 µg/dL (Mahaffey et al. 1982). In children and adolescents, serum levels of 1,25-dihydroxycholecalciferol were negatively associated with PbB over a range of 30–120 µg/dL (Mahaffey et al. 1982). Similar results were observed for vitamin D in children with PbB >50 µg/dL (Rosen et al. 1980). However, in children with PbB <10 µg/dL, no associations between PbB and vitamin D levels were observed (Kemp et al. 2007) (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*). Studies investigating associations between PbB and other endocrine outcomes (salivary cortisol levels, serum levels of growth factors and diabetes) were conducted in populations with PbB ≤10 µg/dL (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*).

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies of endocrine effects associated with PbB ≤10 µg/dL have examined thyroid function, as assessed by serum levels of thyroid hormones (Abdelouahab et al. 2008; Chen et al. 2013; Dundar et al. 2006; Iijama et al. 2007; Luo and Hendryx 2014; Mendy et al. 2013; Yorita Christensen 2013), cortisol levels and cortisol responses to stress (Braun et al. 2014; Gump et al. 2008), vitamin D levels (Kemp et al. 2007), IGF-1 levels (Fleisch et al. 2013), and diabetes (Moon 2013); study details are summarized in *Supporting Document for Epidemiological Studies for Lead*, Table 7. Studies examining thyroid function, including several large cross-sectional studies of NHANES populations (Chen et al. 2013; Mendy et al. 2013; Luo and Hendryx 2014; Yorita Christensen 2013), report inconsistent results; see Table 2-25. Results of NHANES studies at low PbB

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(range of means: 0.93–1.82 µg/dL) are mixed, showing decreased total T4 and no change for free T4 (Mendy et al. 2013; Yorita Christensen 2013), and no change for total or free T4 (Chen et al. 2013; Luo and Hendryx 2014). The NHANES studies did not show associations between PbB and T3 or TSH levels, except for an increase in FT3 (Luo and Hendryx 2014). In smaller studies, decreased TSH and increased free T4 were observed at PbB of 3.10 and 7.3 µg/dL, respectively (Abdelouahab et al. 2008; Dundar et al. 2006). In a large, cross-sectional study, increased TPO antibodies were observed in women with PbBs >2.9 µg/dL, with a significant positive trend (p=0.008) for increased TSH; in men, there was no association (Nie et al. 2017). Thus, few effects on measures of thyroid function have been observed at PbB ≤10 µg/dL, and results do not demonstrate consistent patterns of effects or exposure-response relationships. Results of studies examining other endocrine effects associated with PbB have not been corroborated. Study findings include: associations between PbB and decreased cortisol awakening response during pregnancy at PbB ≥5.1 µg/dL (Braun et al. 2014); enhanced salivary cortisol response to cold stress in children at PbB 1.1–6.2 µg/dL (Gump et al. 2008); no association between PbB and basal cortisol levels or cortisol levels under stress (Ngueta et al. 2018); no association between PbB and serum vitamin D in children at PbB means 4.94–6.54 µg/dL (Kemp et al. 2007); decreased serum IGF-1 in children at PbB 5–9 µg/dL (Fleisch et al. 2013); and no association between PbB and diabetes in children at mean PbB 4.08 µg/dL (Moon 2013).

Mechanisms of Action. Adverse effects on the endocrine system (non-reproductive effects) associated with chronic Pb exposure have not been established; therefore, mechanisms of toxicity have not been identified. Thyroid function could be decreased through stimulation of autoimmunity to the thyroid gland, as shown by increased thyroid peroxidase antibodies (Kahn et al. 2014). In addition, general mechanisms of toxicity (reviewed in Section 2.21) of Pb would likely be involved in any endocrine toxicity.

2.15 IMMUNOLOGICAL

Overview. This section of the profile summarizes the immunological effects of Pb, exclusive of asthma, which is summarized in Section 2.5. Studies conducted in animal models have shown that Pb can perturb the humoral and cell-mediated immune systems, leading to decreased resistance to disease, sensitization, autoimmunity, and inflammation (EPA 2014c). These studies support epidemiological evidence of associations between Pb exposures (as indexed to PbB) and changes in biomarkers of humoral and cell-mediated immunity.

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The following immunological effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Increases in susceptibility to infections.
 - Sensitization to allergens.
 - Changes in indicators of humoral immunity (immunoglobulins, B-cells); demonstrated in several studies.
 - Changes in indicators of cell-mediated immunity (T-cells, eosinophils, neutrophils); demonstrated in several studies.
 - Changes in indicators of inflammatory response (circulating inflammation cytokines).
- > 10 $\mu\text{g/dL}$:
 - Changes in indicators of humoral immunity (immunoglobulins, B-cells).
 - Changes in indicators of cell-mediated immunity (T-cells, natural killer [NK]-cells, neutrophils).
 - Changes in indicators of inflammatory response (inflammatory response of activated monocytes).
 - Decreases in circulating complement.

Measures of Exposure. Studies of associations between Pb exposure and immunological outcomes have relied on PbB as a biomarker of exposure. Most studies have been cross-sectional in design, which increases uncertainty in the interpretation of the results since the exposure history of the subjects is not necessarily indicated by the cross-sectional PbB measurement.

Confounding Factors and Effect Modifiers. The immune system is responsive to a multitude of environmental and physiological factors, which can be confounding factors or effect modifiers in studies of associations between Pb exposure and immunological outcomes. Factors that have been considered in some studies, but not consistently across studies, include age, sex, smoking, physical activity, allergen exposures, history of inflammatory disease, SES factors, recreational activities, and co-exposures to other chemicals. Immunological outcomes observed in epidemiological studies may also be secondary to other systemic effects of Pb (e.g., hematological, splenic gene expression) that affect the immune system.

Characterization of Effects. Table 2-26 lists epidemiological studies that have found associations between PbB and immunological outcomes, grouped by population PbB (typically mean or geometric

mean). Several studies have found alterations in immunological endpoints in association with PbB over the range <10–>50 µg/dL.

Table 2-26. Overview of Immunological Effects Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased susceptibility to infections	Krueger and Wade 2016; Park et al. 2019
	Sensitization to allergens	Jedrychowski et al. 2011; Pizent et al. 2008
	Changes in indicators of humoral immunity ^a	Hon et al. 2009, 2010; Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014; Xu et al. 2015
	Changes in indicators of cell-mediated immunity ^b	Boscolo et al. 2000; Conterato et al. 2013; Hsiao et al. 2011; Karmaus et al. 2005; Sarasua et al. 2000; Wells et al. 2014
	Changes in indicators of inflammatory response ^c	Kim et al. 2007, Sirivarasai et al. 2013; Songdej et al. 2010
>10–30	Changes in indicators of humoral immunity ^a	Heo et al. 2004, Lutz et al. 1999; Sun et al. 2003; Wang et al. 2017a
	Changes in indicators of cell-mediated immunity ^b	Alomran and Shleamoon 1988; Bergeret et al. 1990; Boscolo et al. 1999; Di Lorenzo et al. 2006; Fischbein et al. 1993; Kimber et al. 1986; Mishra et al. 2003; Queiroz et al. 1993, 1994; Sata et al. 1998; Valentino et al. 1991, 2007; Zhao et al. 2004
	Changes in indicators of inflammatory response ^c	Valentino et al. 2007
>30–50	Changes in indicators of humoral immunity ^a	Ewers et al. 1982; Heo et al. 2004; Pinkerton et al. 1998
	Changes in indicators of cell-mediated immunity ^b	Conterato et al. 2013; Fischbein et al. 1993; Garcia-Leston et al. 2012; Niu et al. 2015; Pinkerton et al. 1998
>50	Changes in indicators of humoral immunity ^a	Basaran and Undeger 2000
	Changes in indicators of cell-mediated immunity ^b	Basaran and Undeger 2000; Mishra et al. 2010; Undeger et al. 1996
	Decreases in circulating complement levels	Ewers et al. 1982; Undeger et al. 1996

^aImmunoglobulins, B-cells.

^bT-cells, natural killer (NK) cells, eosinophils, neutrophils and related receptors and cytokines.

^cCirculating cytokines (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNFα]).

Humoral immunity. Numerous epidemiological studies have examined associations between Pb exposure and circulating levels of immunoglobulins. These studies provide evidence that exposure to Pb is associated with increases in circulating IgE in children (Hon et al. 2009, 2010; Karmaus et al. 2005; Lutz

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et al. 1999; Sun et al. 2003; Wang et al. 2017a) and in adults (Heo et al. 2004; Sarasua et al. 2000). IgE is an important mediator of hypersensitivity reactions and inflammation and Pb-induced perturbations in IgE may contribute to associations between Pb exposure and sensitization and inflammation. Although some studies have found changes in levels of other immunoglobins, the evidence for these effects is not as strong as for IgE (Alomran and Shleamoon 1988; Anetor and Adeniyi 1998; Ewers et al. 1982; Kimber et al. 1986; Pinkerton et al. 1998; Queiroz et al. 1994b; Ündeger et al. 1996). The association between circulating IgE levels and PbB appears to extend to PbB levels $<10 \mu\text{g/dL}$ (Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014).

T-cells. T-cells are important mediators of immunity to self-cells (e.g., cancer cells and cells infected with virus) and for activation of B-cells and humoral immunity. Epidemiological studies provide evidence that exposure to Pb is associated with decreases in T-cell abundance in children (Karmaus et al. 2005; Lutz et al. 1999; Sarasua et al. 2000; Zhao et al. 2004) and increases in abundance in adults (Boscolo et al. 1999, 2000; Sarasua et al. 2000). Several studies in adults found no consistent effect on T-cell abundance (Fischbein et al. 1993; Mishra et al. 2010; Pinkerton et al. 1998; Ündeger et al. 1996; Yücesoy et al. 1997b). Most of the studies on T-cell abundance did not differentiate specific classes of T-cell population affected; however, evidence is stronger for effects on CD3+ cells (Karmaus et al. 2005; Lutz et al. 1999; Sarasua et al. 2000; Zhao et al. 2004), with some studies finding effects on abundances of CD4+ (T helper) or CD8+ (T cytotoxic) cells (Boscolo et al. 1999, 2000; Karmaus et al. 2005; Sarasua et al. 2000). The association between circulating T-cell abundance and PbB appears to extend to PbB levels $\leq 10 \mu\text{g/dL}$ (Boscolo et al. 2000; Karmaus et al. 2005; Sarasua et al. 2000).

Neutrophils. Neutrophils are phagocytic cells that function in the immune defense against bacterial infections. Epidemiological studies have found associations between Pb exposure and neutrophil function. The effects on cultured human PMNs in populations that had mean PbB $>10 \mu\text{g/dL}$ includes suppression of chemotaxis, phagocytosis, respiratory oxidative burst, and antigen killing (Alomran and Shleamoon 1988; Bergeret et al. 1990; Fischbein et al. 1993; Kimber et al. 1986; Queiroz et al. 1993, 1994; Valentino et al. 1991). In a worker population having mean PbB $\leq 10 \mu\text{g/dL}$, increasing PbB was associated with decreases in circulating neutrophil abundance (Conterato et al. 2013), whereas in a worker population having mean PbB $>10 \mu\text{g/dL}$, PbB was associated with increases in neutrophil abundance (Di Lorenzo et al. 2006) and decreases in circulating complement levels (Ewers et al. 1982; Undeger et al. 1996).

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NK cells. NK cells contribute to the immune defense (cytotoxicity) against tumor cells and viral infected cells. Although a few studies have found associations between PbB and NK cell abundance (Boscolo et al. 1999, 2000), most studies have found no associations (Fischbein et al. 1993; Garcia-Leston et al. 2011; Karmaus et al. 2005; Kimber et al. 1986; Mishra et al. 2003; Pinkerton et al. 1998; Sarasua et al. 2000; Undeger et al. 1996; Yucesoy et al. 1997) at population mean PbBs ≤ 10 or >10 $\mu\text{g/dL}$.

Lymphocyte activation. A few epidemiological studies have found associations between exposure to Pb and increased lymphocyte activation (HLA-DR expression) and proliferation in children (Lutz et al. 1999) and adults (Alomran and Shleamon 1988; Boscolo et al. 1999; Cohen et al. 1989; Fischbein et al. 1993; Kimber et al. 1986; Mishra et al. 2003). These studies found effects in populations that had PbB >10 $\mu\text{g/dL}$.

Sensitization. Epidemiological studies provided evidence for associations between exposure to Pb and sensitization. This evidence includes increased risk of atopy to airborne allergens in children (Jedrychowski et al. 2011) and adults (Pizent et al. 2008). Consistent with findings in animal studies which found that Pb exposure suppresses delayed type hypersensitivity (DTH), Hsiao et al. (2011) found that higher PbB was associated with decreases in circulating levels of IFN- γ γ T-helper cytokine known to be important in DTH). The above effects related to sensitization have been observed in populations that had mean PbB ≤ 10 $\mu\text{g/dL}$.

Inflammation. A few epidemiological studies have examined possible associations between Pb exposure and biomarkers of inflammation. Results for these studies suggest that Pb exposure can modify the control of inflammatory responses, including modifying macrophage NO release and ROS production in macrophages harvested from exposed children (Pineda-Zavaleta et al. 2004), and in adults, decreases in abundance of circulating monocytes (Conterato et al. 2013; Pinkerton et al. 1998), and lower circulating levels of HLA-DR+ (Fischbein et al. 1993) in adults. Three studies found evidence for effects indicative of enhancement or stimulation of inflammation in adults at mean PbB ≤ 10 $\mu\text{g/dL}$. Outcomes included increases in circulating tumor necrosis factor-alpha (TNF α) (Kim et al. 2007) and C-reactive protein (CRP) in men (Songdej et al. 2010; Sirivarasai et al. 2013).

Effect at Blood Pb Levels ≤ 10 $\mu\text{g/dL}$. Epidemiological studies that have evaluated immunological effects associated with PbB ≤ 10 $\mu\text{g/dL}$ are summarized in Table 2-27, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 8. Outcomes that have been observed in populations with PbB ≤ 10 $\mu\text{g/dL}$ include susceptibility to infections, sensitization in children and

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adults, humoral and cell-mediated immunity in children and adults, and inflammation in children and adults.

Susceptibility to infections. A cross-sectional study of data from NHANES (1999–2012) found a trend for increasing OR for being seropositive for *H. pylori*, *T. gondii*, and *Hepatitis B* virus in a population that has a geometric mean PbB of 1.5 µg/dL (Krueger and Wade 2016).

Humoral immunity. Several studies have found associations between circulating IgE levels and PbB in populations with mean or geometric mean PbB levels ≤ 10 µg/dL (Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014). In general, these studies found increases in serum IgE levels in association with increasing PbB in children (Karmaus et al. 2005; Sarasua et al. 2000; Wang et al. 2017a; Wells et al. 2014) and adults (Min and Min 2015; Pizent et al. 2008). A cross-sectional study of children (3–7 years of age) found an association between increasing PbB and decreasing *Hepatitis B* virus antibody titers (Xu et al. 2015).

T-cells, neutrophils, and NK cells. Several studies have found associations between T-cell abundance and PbB in populations with mean or geometric mean PbB levels ≤ 10 µg/dL. In studies of children, T-cell abundances decreased (Karmaus et al. 2005), whereas in a study of adults, T-cell abundance increased (Boscolo et al. 2000). In a study of Pb workers, neutrophil abundance was lower in Pb workers compared to controls (Contertato et al. 2013). The worker populations included a group of painters in which the mean PbB was 5.4 ± 0.4 (SE) µg/dL, compared to the control group (1.5 ± 0.1 , SE). A study of a population of atopic adult women with median PbB 6.6 µg/dL (25th–75th percentile range: 4.9–7.9), found an association between increasing PbB and increasing abundance of NK cells (CD4+CD45RO+; Boscolo et al. 2000).

Sensitization. Exposures to Pb that resulted in population geometric mean PbB ≤ 10 µg/dL was associated with increased risk of atopy to airborne allergens in children (Jedrychowski et al. 2011) and adults (Pizent et al. 2008). Higher PbB was associated with decreases in circulating levels of IFN-γ (a T-helper cytokine known to be important in DTH) in a population of children with a mean PbB of 8.8 ± 0.45 (SD) µg/dL (Hsaio et al. 2011).

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Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^b
Sensitization			
Jedrychowski et al. 2011	Gmean (95% CI): Cord: 1.16 (1.12, 1.22)	Atopy	Adjusted RR: • Cord PbB: 2.28 (1.12, 4.62)* • Maternal PbB: 1.72 (0.98, 3.00)
Prospective study; n=224 children (at 5 years of age) of women recruited in the 2 nd trimester of pregnancy	Maternal: 1.60 (1.52, 1.67)		
Pizent et al. 2008	Gmean (95% CI): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35)	SPT	Adjusted OR for positive SPT: 0.92 (0.86, 0.98)*
Cross-sectional study; n=216 adults (age range 19–67 years)			
Humoral immunity			
Karmaus et al. 2005	Gmean (95% CI): • Males: 2.78 (1.48, 4.82) • Females: 2.54 (1.10, 4.38)	IgE	Mean serum IgE levels were higher ($p \leq 0.05$) in PbB strata > 2.84 and > 3.41 $\mu\text{g/dL}$ *
Cross-sectional study; n=671 children (age 7–10 years)		B-cells	B-cell abundance was lower ($p \leq 0.05$) in PbB stratum 2.21–2.83 compared to < 2.2 $\mu\text{g/dL}$ *
Min and Min 2015	Gmean (95% CI): • 1.46 (1.44, 1.50)	IgE	β for 1 log ₁₀ increase in IgE per 1 log ₁₀ increase in PbB: • Q2 (1.1–1.69 $\mu\text{g/dL}$): 0.20 (0.05, 0.34)* • Q3 (1.7–2.6 $\mu\text{g/dL}$): 0.26 (0.10, 0.42)* • Q4 (2.61–26.4 $\mu\text{g/dL}$): 0.35 (0.20, 0.51)*
Cross-sectional study; n=4,287 adults (age ≥ 22 years) ^c			
Pizent et al. 2008	Gmean (95% CI): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35)	IgE	β log increase in IgE per log increase in PbB $\mu\text{g/L}$ (SE), females not taking oral contraceptives or hormone replacement therapy: 0.600 (0.298); $p=0.046$ *
Cross-sectional study; n=216 adults (age range 19–67 years)			

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Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Sarasua et al. 2000	Gmean (95% CI):	IgA	β per 1 µg/dL PbB, age 6–35 months: 0.8, p<0.01*
Cross-sectional study;	• Age 6–35 months:	IgG	• β per 1 µg/dL PbB, age 6–35 months: 0.8;
n=1,561 residents of communities	7.0 (1.7, 16.1)		p<0.01*
with elevated levels of Cd or Pb in	• Age 36–71 months:		• β per 1 µg/dL PbB, age 6–15 years: 7.5;
soil (age range 6 months–75 years)	6.0 (1.6, 14.1)		p=0.02*
(1991)	• Age 6–15 years:	IgM	β per 1 µg/dL PbB, age 6–35 months: 1.0; p=0.03*
	4.0 (1.1, 9.2)	B-cell count	β per 1 µg/dL PbB, age 6–35 months: 16.9;
			p<0.01*
		B-cell%	β per 1 µg/dL PbB, age 6–35 months: 0.19;
			p=0.02*
Wang et al. 2017a	PbB Gmean (GSD)	IgE	• All participants, β per ln-unit increase in PbB (2.72 µg/dL): 0.26 (0.009, 0.50); p=0.042*
Cross-sectional study; n=930 children	• All: 1.86 (1.21)		• Boys, β per ln-unit increase in PbB (2.72 µg/dL): 0.40 (0.03, 0.76); p=0.036*
(mean age: 5.74 years; 469 boys and	• Boys: 1.88 (1.22)		• Girl, β per ln-unit increase in PbB (2.72 µg/dL):
461 girls)	• Girls: 1.83 (1.20)		0.02 (-0.35, 0.40); p=0.901
Wells et al. 2014	Gmean (95% CI):	IgE	β per 1 µg/dL PbB for % increase per 1 µg/dL:
Cross-sectional study;	• 1.13 (1.04, 1.22)		10.27 (3.52, 17.47)*
n=1,788 children (age 2–12 years) ^c			
Xu et al. 2015	Gmean (SD of log PbB):	Hepatitis B virus	Antibody titers decreased with increasing PbB
Cross-sectional study; n=590 children	• Male: 6.61 (0.19)		β signal to cut-off ratio per 1 µg/dL (SE) at two
(age 3–7 years)	• Female: 6.16 (0.18)		assessment dates:
			• 2011: -0.4467 (0.0225); p<0.001*
			• 2012: 0.3661 (0.0193); p<0.001*

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Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^b
Cell-mediated immunity			
Boscolo et al. 2000	Median:	T-cell abundance	Positive correlation between PbB and T-cell abundances in non-atopic subjects (r for cell count):
Cross-sectional study; n=30 atopic women (age range 19–49 years) and 30 non-atopic women	<ul style="list-style-type: none"> Atopic: 6.4 (4.9, 7.9) Control: 5.5 (4.4, 6.7) 		<ul style="list-style-type: none"> CD4+CD45RO-: 0.464; $p<0.05^*$ CD3+ CD8+: 0.430; $p<0.05^*$ CD3- HLA-DR+: 0.435; $p<0.05^*$
Conterato et al. 2013	Median:	Neutrophil abundance	Mean (SE), $10^3/\text{mm}^3$:
Cross-section study of battery manufacture workers (n=59), and automobile painters (n=23); ages 15–61 years	<ul style="list-style-type: none"> Battery workers: 49.8 (4.0) Painters: 5.4 (0.4) Controls: 1.5 (0.1) 		<ul style="list-style-type: none"> Battery workers: 2.87 (0.27); $p<0.05^*$ Painters: 3.07 (0.13); $p<0.05^*$ Controls: 3.75 (2.49)
Hsiao et al. 2011	Mean (SD):		Compared to all other groups, allergic group residing near the refinery had:
Cross-sectional study; n=214 children (primary school grades 5–6)	<ul style="list-style-type: none"> Allergic and residing near oil refinery: 8.80 (0.45) Non-allergic and residing near oil refinery: 5.23 (0.36) Other rural or urban groups, allergic or not: 3.16–3.83 	IFN- γ	>96% decrease in serum IFN-γ; $p<0.05^*$
		IL-12	>96% decrease; $p<0.05^*$
		IL-4	>500% increase; $p<0.05^*$
		IL-25	>500% increase; $p<0.05^*$
Karmaus et al. 2005	Gmean (95% CI):	T-cell and T _c	Lower ($p\leq 0.05$) in PbB stratum 2.21–2.83 compared to <2.2 $\mu\text{g}/\text{dL}^*$
Cross-sectional study; n=67 children (age 7–10 years)	<ul style="list-style-type: none"> Males: 2.78 (1.48, 4.82) Females: 2.54 (1.10, 4.38) 		

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Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Sarasua et al. 2000	Gmean (95% CI):L):	T-cell%	β per 1 µg/dL PbB: -0.18; p=0.03*
Cross-sectional study; n=1,561; age range 6 months–75 years)	Age	T-cell count	β per 1 µg/dL PbB: 7.2; p=0.59
	• 6–35 months: 7.0 (1.7, 16.1)	NK-cell%	β per 1 µg/dL PbB: 0.00; p=0.99
	• 36–71 months: 6.0 (1.6, 14.1)	NK-cell count	β per 1 µg/dL PbB: 1.3; p=0.60
	• Age 6–15 years: 4.0 (1.1, 9.2)		
Wells et al. 2014	Gmean (95% CI):	Eosinophils %	β for % increase per 1 µg/dL: 4.61 (2.44, 6.83)*
Cross-sectional study; n=1,788 children (age 2–12 years) ^c	1.13 (1.04, 1.22)		
Inflammation			
Kim et al. 2007	Mean (range):		In males for PbB stratum >2.51 relative to lower PbB stratum. % per 1 µg/dL increase in PbB:
Cross-sectional study; n=300 adults (mean age 24±2 years)	• Q1: 1.46 (0.337, 1.885)	TNFα	23% (4, 55); p=0.015*
	• Q2: 2.22 (1.886, 2.511)	WBC	15% (0, 35); p=0.004*
	• Q3: 2.77 (2.513, 3.103)	IL-6	26% (0, 55%); p=0.082
	• Q4: 3.93 (3.110, 10.470)	CRP	CRP was higher in upper quartile PbB stratum compared to Q1 and Q2 (p<0.001). In Q4 stratum, adjusted OR was elevated for GSTM1 and GSTT1 null genotypes:
Sirivarasai et al. 2013	Mean: 5.45		• -GSTM1-/- and GSTT1-/-: 1.98 (1.47, 2.55)*
Cross-sectional study; n=924 male adults (mean age 43 years)	Quartiles, mean (range):		• -GSTM1-/-: 1.32 (1.03, 1.69)*
	• Q1: 2.44 (1.23, 3.47)		• -GSTT1-/-: 1.65 (1.17, 2.35)*
	• Q2: 3.95 (3.48, 4.55)		
	• Q3: 5.77 (4.56, 6.47)		
	• Q4: 9.21 (6.48, 24.62)		

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Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result ^b
Songdej et al. 2010	Gmean: 1.89		OR for <1.16 versus >3.09 µg/dL:
Cross-sectional study; n=9,145 adults (age >40 years) ^c	CRP	• Males: 2.85 (1.49, 5.45)*	
		• Females: 0.57 (0.43, 0.76)	
	Fibrinogen	• Males: 1.15 (0.61, 2.16)	
		• Females: 0.87 (0.57, 1.33)	
	WBC	• Males: 1.55 (0.96, 2.49)	
		• Females: 0.84 (0.62, 1.13)	

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 8 for more detailed descriptions of studies.

^bAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

^cStudy of NHANES participants.

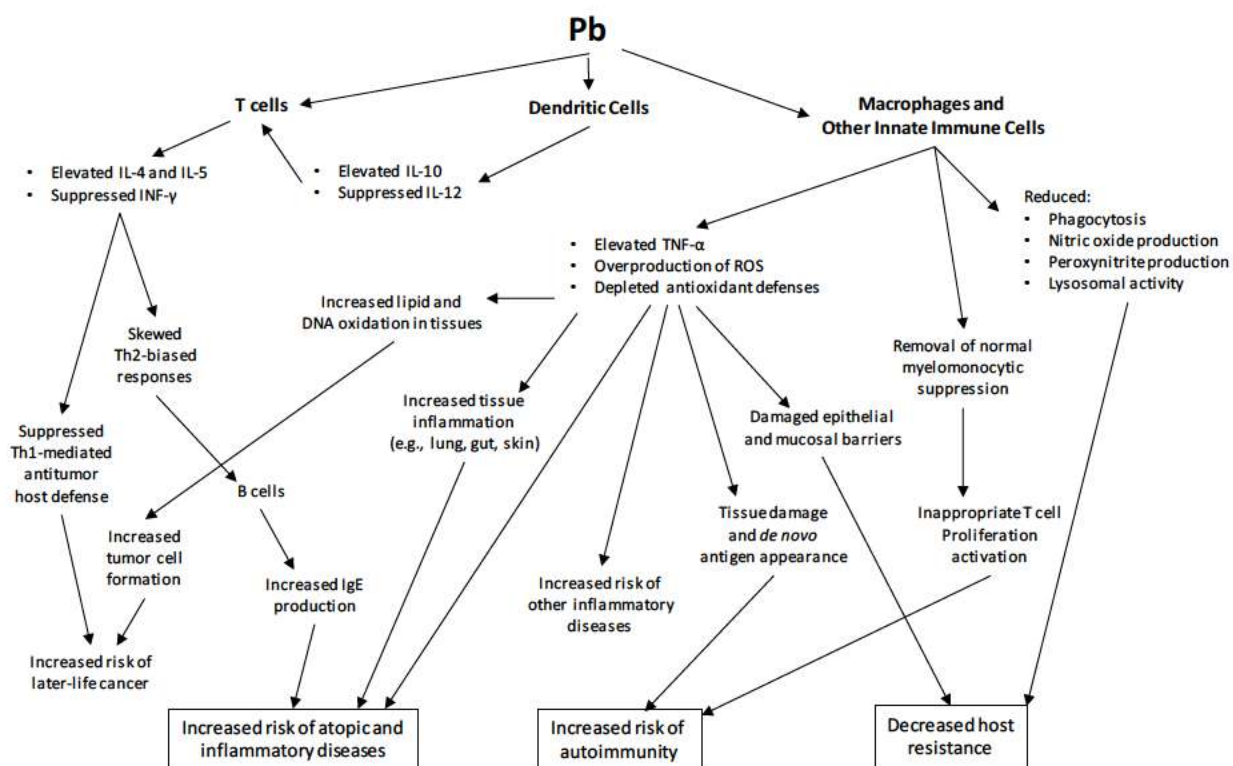
Cd = cadmium; CI = confidence interval; CL = confidence limit; CRP = C-reactive protein; Gmean = geometric mean; GSTM1 = glutathione S-transferase Mu 1; GSTT1 = glutathione S-transferase theta 1; IFN-γ = interferon gamma; Ig = immunoglobulin antibody; IL = interleukin; NHANES = National Health and Nutrition Examination Survey; NK = natural killer; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error; SPT = skin prick test; TNFα = tumor necrosis factor-alpha; WBC = white blood cell

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Inflammation. A few studies have found evidence for increases in circulating TNF α (Kim et al. 2007) and CRP (Songdej et al. 2010; Sirivarasai et al. 2013) in adults at mean PbB <10 μ g/dL. These outcomes are indicative of enhancement or stimulation of inflammation.

Mechanisms of Action. Studies conducted in animal models and cell cultures have shown that Pb can disrupt the immune response through diverse mechanisms (EPA 2014c). Figure 2-6 shows the various potential pathways by which Pb may perturb the immune system and increase risk of atopy and inflammation, autoimmunity, and host resistance. In addition to its effects on T-cells, dendritic cells, and macrophages, Pb may also alter immune function at many other processes in the pathways shown in Figure 2-6.

Figure 2-6. Immunological Pathways by which Pb Exposure Potentially may Increase Risk of Immune-Related Diseases



Note: As shown in the figure, immunological pathways may increase risk of diseases such as cancer and inflammatory diseases in the cardiovascular, renal, and hepatic systems.

Source: EPA 2014c

2.16 NEUROLOGICAL

Overview. The literature on the neurobehavioral effects of Pb is extensive. With the improvement in analytical methods to detect Pb in the various biological media and in study designs, the concentrations of Pb, particularly in blood, associated with alterations in neurobehavioral outcomes continue to decrease, suggesting that there may be no threshold for the effects of Pb on intellectual function (CDC 2012d). Due to the enormous size of the database on neurobehavioral effects of Pb, this discussion has been limited to representative and/or major studies published on specific topics crucial to understanding dose-response relationships in the lower exposure ranges (e.g., PbB ≤ 10 $\mu\text{g/dL}$). For additional information, the reader is referred to a recent review of this topic (EPA 2014c).

Numerous epidemiological studies have evaluated effects of Pb on neurological function in children and adults. These studies show consistent evidence of associations between decrements in cognitive and neuromotor/neurosensory function with PbBs that range from ≤ 10 to >50 $\mu\text{g/dL}$. The PbB-effect relationship for cognitive effects in children extends well below 10 $\mu\text{g/dL}$, with no evidence for a threshold. In several PbB-effect models, the slope for decrements in cognitive function in children show greater increases at lower PbB ranges. These models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 $\mu\text{g/dL}$, than when PbB increases to levels >10 $\mu\text{g/dL}$. All of the cognitive and neurobehavioral effects of Pb observed in children have also been observed in adults; however, it is not certain what life-stage exposures contribute most to outcomes in adults. A few studies that have followed children to early adulthood provide evidence of associations between childhood Pb exposure (e.g., PbB) and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Other studies have found evidence of associations between cumulative Pb exposures (e.g., bone Pb) and neurological outcomes in adults.

The following neurobehavioral effects in children have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Decreased cognitive function including full scale IQ (FSIQ).
 - Altered mood and behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
 - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, and hearing threshold.

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- >10 µg/dL:
 - Decreased cognitive function including FSIQ.
 - Altered mood and behaviors, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
 - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, hearing threshold, and visual evoked potentials.
 - Peripheral neuropathy.
 - Encephalopathy.

The following neurobehavioral effects in adults have been associated with increasing PbB:

- ≤10 µg/dL:
 - Decreased cognitive function including attention, memory, and learning.
 - Altered neuromotor and neurosensory function including decreased reaction time and walking speed, tremor, and increased risk of amyotrophic lateral sclerosis (ALS).
 - Altered mood and behavior including risk of various psychiatric symptoms including anxiety, depression, and schizophrenia.
- >10 µg/dL:
 - Reduced brain volume and altered brain neurochemistry.
 - Decreased cognitive function.
 - Altered neuromotor and neurosensory function.
 - Decreased peripheral nerve conduction velocity.

Measures of Exposure. Studies conducted in children have relied heavily on PbB as an exposure metric. Although bone or tooth Pb measurements may be informative, few studies have been conducted in children (Bellinger et al. 1994; Campbell et al. 2000b; Fergusson et al. 1993; Kim et al. 1995; Needleman et al. 1979, 1990, 1996, 2002; Wasserman et al. 2003). Maternal bone Pb has been used as an exposure metric for evaluating outcomes in children (Gomaa et al. 2002; Xu et al. 2015). Bone Pb has been used as metric of cumulative exposure in a growing number of epidemiological studies of adults (see Section 3.3.1, Biomarkers of Exposure). An association between a health outcome and bone Pb does not necessarily infer an association between the outcome and PbB (or *vice versa*) as indicated by studies in which associations are not consistent for the two metrics. These differences may reflect the relative importance of cumulative exposure on the given outcome, or differences in error associated with measurements of blood and bone Pb concentrations. A review by Shih et al. (2007) concluded that

negative associations between Pb and cognitive function are stronger for bone Pb (specifically tibia Pb) for environmental exposures and for PbB for occupational exposures.

Confounding Factors and Effect Modifiers. Various factors have the potential to contribute to bias in estimates of associations between PbB and neurobehavioral outcomes. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome. Neurological function can be influenced by numerous factors that may also correlate with Pb exposure in the population studied. A contributor to these correlations is the influence of SES-related factors on Pb exposure. Confounding factors that are typically evaluated in all high-quality studies include maternal education and IQ, SES, and HOME score (parental care). However, other factors have also been explored in some studies, including maternal substance abuse (including prenatal alcohol) and psychopathology, birth weight, exposure to tobacco smoke, nutritional status, and ALAD allele type. The relatively strong correlation between SES and PbB can result in overcontrol in studies of populations that have wide SES variability. Overcontrol will tend to attenuate the estimated association between PbB and the outcome (Bellinger 2004). However, SES may also modify the effect of Pb on neurological function (Bellinger et al. 1990; Ris et al. 2004; Tong et al. 2000). If this were to occur, then SES would also be an effect-modifier.

Characterization of Effects in Children. A large number of studies showing decrements in neurological function in children have been published (Table 2-28). Collectively, these studies support the concept that Pb affects cognitive function in children prenatally exposed to PbB ≤ 10 $\mu\text{g/dL}$, with numerous studies providing evidence for effects at PbB ≤ 5 $\mu\text{g/dL}$. Neurobehavioral functions that have been associated with PbB ≤ 10 $\mu\text{g/dL}$ include decrements in cognitive function (learning and memory), altered behavior and mood (e.g., attention, hyperactivity, impulsivity, irritability, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These outcomes also have been observed in association with PbB > 10 $\mu\text{g/dL}$. In children who have been followed to early adulthood, mean childhood PbBs of 13 $\mu\text{g/dL}$ were associated with altered brain volume and neurochemistry (Brubaker et al. 2010; Cecil et al. 2008, 2011). PbBs > 30 $\mu\text{g/dL}$ are associated with a variety of decrements in cognitive function, behavior (e.g., depression, aggression), and nerve function (e.g., decrements in fine and gross motor skills, peripheral neuropathy). Encephalopathy has been observed in children who have experienced severe Pb poisoning typical of PbB > 80 $\mu\text{g/dL}$ (NAS 1972).

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Table 2-28. Overview of Neurological Effects in Children Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Intellectual deficits ^a	Blackowicz et al. 2016; Baghurst et al. 1992; Bellinger and Needleman 2003; Bellinger et al. 1992; Boucher et al. 2014; Braun et al. 2012; Canfield et al. 2003; Chandramouli et al. 2009; Chiodo et al. 2004; Desrochers-Couture et al. 2018; Dietrich et al. 1986, 1987, 1989, 1991, 1992, 1993a; Emory et al. 2003; Evens et al. 2015; Geier et al. 2017; Gomaa et al. 2002; Hong et al. 2015; Hu et al. 2006; Jedrychowski et al. 2009; Jusko et al. 2008; Kordas et al. 2011; Krieg et al. 2010; Lanphear et al. 2000a, 2005, 2019; Lin et al. 2013; Liu et al. 2014b; Mazumdar et al. 2011; McLaine et al. 2013; Min et al. 2009; Miranda et al. 2009; Polanska et al. 2018; Rodrigues et al. 2016; Rooney et al. 2018; Ruebner et al. 2019; Schnaas et al. 2006; Shadbegian et al. 2019; Sobin et al. 2015; Tellez-Rojo et al. 2006; Vigeh et al. 2014; Wang et al. 2008; Wasserman et al. 1994, 1997, 2003; Zhang et al. 2013; Zhou et al. 2017
	Altered mood and behavior ^b	Arbuckle et al. 2016; Boucher et al. 2012; Braun et al. 2006, 2008; Choi et al. 2016; Dietrich et al. 2001; Froehlich et al. 2009; Fruh et al. 2019; Geier et al. 2018; He et al. 2019; Hong et al. 2015; Huang et al. 2016; Ji et al. 2018; Joo et al. 2017, 2018; Kim et al. 2013a, 2016; Liu et al. 2014a, 2015b; Park et al. 2016; Sioen et al. 2013; Stroustrup et al. 2016; Wang et al. 2008; Winter and Sampson 2017
	Altered neuromotor neurosensory function ^c	Chiodo et al. 2004; Dietrich et al. 1987, 1989, 1993b; Ethier et al. 2012; Fraser et al. 2006; Kim et al. 2013b; Liu et al. 2018b; Osman et al. 1999; Silver et al. 2016; Tellez-Rojo et al. 2006
	Altered brain anatomical development and activity	Cecil et al. 2008, 2011
>10–30	Intellectual deficits ^a	Baghurst et al. 1992; Bellinger et al. 1987, 1990, 1991; Chen et al. 2005, 2007; Dietrich et al. 1992, 1993a; Factor-Litvak et al. 1999; Hornung et al. 2009; Kordas et al. 2006; Magzamen et al. 2013, 2015; Marques et al. 2014; McMichael et al. 1988; Roy et al. 2011; Schnaas et al. 2000; Shen et al. 1998; Tong et al. 1996; Wasserman et al. 1994, 1997, 2000, 2003
	Altered mood and behavior ^b	Amato et al. 2013; Chen et al. 2007; Dietrich et al. 1993b, 2001; Lin et al. 2019; McFarlane et al. 2013; Neugebauer et al. 2015; Nkomo et al. 2017; Rothenberg et al. 1989; Roy et al. 2009; Wu et al. 2018
	Altered neuromotor neurosensory function ^c	Baghurst et al. 1995; Bhattacharya et al. 2006; Otto et al. 1985; Palaniappan et al. 2011; Parajuli et al. 2013; Ris et al. 2004; Robinson et al. 1985; Schwartz and Otto 1987, 1991

Table 2-28. Overview of Neurological Effects in Children Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
>30–50	Intellectual deficits ^a	do Nascimento et al. 2014; Royal et al. 2013
>50	Intellectual deficits ^a	Hou et al. 2013
	Altered mood and behavior ^b	Hou et al. 2013
	Altered neuromotor neurosensory function ^c	Hou et al. 2013;
	Peripheral neuropathy ^d	Erenberg et al. 1974; Landrigan et al. 1976; Schwartz et al. 1988; Seto and Freeman 1964
>80	Encephalopathy	NAS 1972

^aIntellectual deficits include decreased IQ, cognitive function, verbal comprehension, language development, perceptual organization, processing speed, decreased math and reading aptitude, educational attainment, school performance, and memory.

^bAltered mood and behavior includes hyperactivity, ADHD, decreased adaptive skills and emotional functioning, externalizing behaviors, internalizing behaviors, social problems, delinquent behavior, impulsive behavior, irritability, autistic behavior, altered sleep, and associations between child PbB and adult behavior (see McFarlane et al. (2013).

^cAltered neuromotor neurosensory function includes decreased integrated motor activities, gross motor skills; fine motor speed and dexterity, and visual-motor integration.

^dPeripheral neuropathy includes decreased motor and sensory nerve conduction velocity.

ADHD = attention-deficit/hyperactivity disorder; IQ = intelligence quotient; PbB = blood lead concentration

Characterization of Effects in Adults. A large number of studies showing decrements in neurological function in adults have been published (Table 2-29). These studies have found neurobehavioral effects in populations whose PbBs were ≤ 10 µg/dL. Neurobehavioral functions that have been associated with PbB ≤ 10 µg/dL include decreased cognitive function, altered behavior and mood, and altered neuromotor and neurosensory function. These outcomes also have been observed in association with PbB >10 µg/dL. PbBs in the range of 10–20 µg/dL, measured either during childhood or in adulthood, have been associated with decreased brain volume and changes in brain neurochemistry (Brubaker et al. 2010; Cecil et al. 2008; 2011; Hsieh et al. 2009). PbBs >30 µg/dL are associated with a variety of decrements in cognitive function, behavior and nerve function, including postural sway and stability; decreased walking speed; decreased visuospatial function and visual-motor performance; decrements in hearing; peripheral neuropathy; psychiatric symptoms (depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia); and changes in regional brain volumes and neurochemistry.

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Table 2-29. Overview of Neurological Effects in Adults Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Intellectual deficits ^a	Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006; Wright et al. 2003b
	Altered mood and behavior ^b	Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Opler et al. 2004; Rajan et al. 2007, 2008; Rhodes et al. 2003
	Altered neuromotor neurosensory function ^c	Hwang et al. 2009; Ji et al. 2013; Krieg et al. 2005
	Neurological diseases (ALS)	Fang et al. 2010
>10–30	Intellectual deficits ^a	Mantere et al. 1982; Reuben et al. 2017
	Altered mood and behavior ^b	Beckley et al. 2018; Yoon and Ahn et al. 2016
	Altered neuromotor neurosensory function ^c	Chuang et al. 2007; Yokoyama et al. 1997
	Altered brain architecture and metabolism	Brubaker et al. 2010; Cecil et al. 2008, 2011; Hsieh et al. 2009
>30–50	Intellectual deficits ^a	Baker et al. 1983; Barth et al. 2002; Campara et al. 1984; Fazli et al. 2014; Goodman et al. 2002; Hogstedt et al. 1983; Meyer-Baron and Seeber 2000; Schwartz et al. 2005; Vlasak et al. 2019
	Altered mood and behavior ^b	Baker et al. 1983; Lucchini et al. 2000; Maizlish et al. 1995; Malekirad et al. 2013; Parkinson et al. 1986
	Altered neuromotor neurosensory function ^c	Baker et al. 1983; Barth et al. 2002; Chia et al. 1996; Choi et al. 2012; Ghiasvand et al. 2016; Haenninen et al. 1978; Iwata et al. 2005
	Altered nerve conduction	Araki et al. 1980, 1987, 2000; Chia et al. 1996; Hirata and Kosaka et al. 1993; Pasternak et al. 1989; Stollery et al. 1989, 1991

Table 2-29. Overview of Neurological Effects in Adults Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
>50	Intellectual deficits ^a	Arnvig et al. 1980; Campara et al. 1984; Fenga et al. 2016; Matte et al. 1989; Valciukas et al. 1978
	Altered mood and behavior ^b	Awad el Karim et al. 1986; Zimmerman-Tansella et al. 1983
	Altered neuromotor neurosensory function ^c	Hanninen et al. 1998
	Altered nerve conduction	Triebig et al. 1984
	Altered brain architecture	Jiang et al. 2008

^aIntellectual deficits include decreased IQ, cognitive function, learning ability, verbal reasoning, logic, memory, and concentration.

^bAltered mood and behavior include depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia.

^cAltered neuromotor neurosensory function includes postural sway; postural stability, decreased walking speed, decreased visuospatial function and visual-motor performance, hearing loss, and altered hearing threshold.

ALS = amyotrophic lateral sclerosis; PbB = blood lead concentration

Effects at Blood Pb Levels ≤ 10 µg/dL in Children. Numerous prospective and large cross-sectional studies provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in children in association with exposures that result in PbB < 10 µg/dL, with some studies showing effects at PbB ≤ 5 µg/dL. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead*, Table 9. The cognitive outcome metric that has been most extensively studied and compared across studies is FSIQ. Tests of memory, learning, and executive function have also been used to assess cognitive function. Studies that attempt to identify associations between PbB and cognitive function must control for major factors known to influence or correlate with cognitive development and function, including SES, parental education and IQ, quality of caregiving, nutrition, and birth weight. Many of these same factors correlate with PbB and can confound associations between PbB and outcomes. Relationships between PbB and outcomes appear to be nonlinear. The Lanphear et al. (2005) pooled analysis and re-analyses (Crump et al. 2013; EPA 2014e) predict a nonlinear dose-response relationship for Pb in which the slope for the decrement in cognitive function in children increases with decreasing PbB. The biological significance of the observed supra-linear response has been the subject of several reviews and commentaries (Bowers and Beck 2006; Hornung and Lanphear 2014; Jusko et al. 2006). Decrements in cognitive function in children have been associated with increasing PbB measured at various life stages, including prenatal and various metrics of

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child PbB including peak, concurrent, and cumulative. No specific life stage has been conclusively identified as the critical time period for exposure.

Cognitive function in infancy. Several prospective studies have evaluated cognitive function in infancy and early child cohorts having mean PbB <10 µg/dL (Table 2-30). In general, these studies provide evidence for decrements in cognitive function in association with increasing PbB. Several studies used the Mental Development Index (MDI) score from the Bayley Scales of Infant Development (BSID), allowing comparison of results across studies (Dietrich et al. 1986, 1987, 1989; Gomaa et al. 2002; Hu et al. 2006; Jedrychowski et al. 2009; Liu et al. 2014b). Each study found decreases in MDI scores measured from 6 to 36 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Cohort mean PbB ranged from 1.2 to 7.1 µg/dL. In a cohort that had a mean PbB of 1.23 µg/dL (range 0.44–6.9 µg/dL), the change in MDI score measured at 24 months of age was -7.6 (95% confidence limit [CL] -14.7, -0.62) points per 1 log₁₀ increase in cord PbB (Jedrychowski et al. 2009). The largest effect size was reported for a cohort that had a mean PbB of 8±3.8 (SD) µg/dL; the change in MDI score measured at age 6 months was -15±5.1 (SE, p<0.03) points per cord lnPbB (Dietrich et al. 1986). Studies that repeatedly measured MDI scores longitudinally within the same birth cohorts found that the associations observed at 6 months persisted to later ages (Dietrich et al. 1986, 1987, 1989, 1991; Jedrychowski et al. 2009; Liu et al. 2014b). The association between Pb and declining cognitive behavior appears to be exacerbated by maternal prenatal psychosocial stress. A small prospective study conducted in Shanghai, China (139 mother-infant pairs) found larger effect sizes on language development in mothers who demonstrated higher prenatal stress (Zhou et al. 2017).

Cognitive function in early childhood - FSIQ. Prospective studies initiated at time of pregnancy or birth have consistently found decrements in child FSIQ in association with increasing cohort mean PbB <10 µg/dL measured at various stages of development (Table 2-30). Collectively, these studies provide evidence for effect sizes ranging from -1 to -6 FSIQ points in association with a 10-fold increase in PbB and larger effect sizes in cohorts or cohort strata having a lower mean PbB. These studies do not consistently point to a specific life stage as being more or less vulnerable, as negative associations with FSIQ have been observed with PbB measured during pregnancy, infancy, and childhood, and measured previous to or concurrently with the FSIQ evaluation. Results of an adult follow-up of a birth cohort suggest that FSIQ decrements observed in childhood may persist to adulthood (Mazumdar et al. 2011).

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Intellectual deficits			
Baghurst et al. 1992		FSIQ	β (SE) for PbB metrics per each 1 µg/dL increase:
Prospective cohort, n=494 children followed from birth to age 7 years	Quartile range: • Birth: 4.3, 15.0 • Mean 0–2 years: 11.6, 27.1 • Mean 0–3 years: 12.2, 28.2 • Mean 0–4 years: 12.2, 27.7 • Lifetime average (7 years): 10.8, 24.8		<ul style="list-style-type: none"> • Prenatal: 0.6 (1.4), p=0.68 • Mean 0–2 years: -4.6 (2.1), p=0.03* • Mean 0–3 years: -4.8 (2.3), p=0.04* • Mean 0–4 years: -4.6 (2.4), p=0.05* • Lifetime average: -3.7 (2.5), p=0.14
Blackowicz et al. 2016		ISAT	RR for failure on ISAT for 1 or 5 µg/dL increase in PbB:
Retrospective study; n=12,319 third-grade Hispanic children	Mean (SD): • 4.16 (2.03)		Reading ISAT: <ul style="list-style-type: none"> • 1 µg/dL increase: 1.07 (1.05, 1.10)* • 5 µg/dL increase: 1.43 (1.25, 1.63)* Math ISAT <ul style="list-style-type: none"> • 1 µg/dL increase: 1.09 (1.06, 1.12)* • 5 µg/dL increase: 1.53 (1.32, 1.78)*
Bellinger et al. 1992; Bellinger and Needleman 2003		FSIQ	β (SE) for PbB metrics per each 1 µg/dL increase in PbB:
Prospective cohort, n=148 children followed from birth to age 10 years	Mean (SE): • 6 months: 6.7 (7.0) • 1 years: 7.7 (6.5) • 2 years: 6.5 (4.9)		<ul style="list-style-type: none"> • Prenatal: -2.55 (2.56), p=0.57 • 6 months: -0.13 (0.15), p=0.39 • 2 years: -0.58 (0.21), p<0.007* • Peak <10 µg/dL: -1.56 (p=0.03)* • Peak >10 µg/dL: -0.58 (p=NA)
Boucher et al. 2014		FTII-fixed duration	β 0.21 (0.07, 0.35); p≤0.01*
Prospective cohort, n=93 infants	Umbilical cord PbB: • Mean (SD): 4.8 (3.5) • Range: 0.5–17.8		

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Chiodo et al. 2004 Prospective study; n=237 children, age 7.5 years	Mean (SD, range): 5.4 (3.3, 1–25)	FSIQ	β (SE): <ul style="list-style-type: none"> • <3 $\mu\text{g/dL}$: -0.10; $p \leq 0.1^*$ • <5 $\mu\text{g/dL}$: -0.12; $p \leq 0.1^*$ • <7.5 $\mu\text{g/dL}$: -0.14; $p \leq 0.05^*$ • <10 $\mu\text{g/dL}$: -0.18; $p \leq 0.01^*$ • Cohort: -0.20; $p \leq 0.01^*$
Desrochers-Couture et al. 2018 Prospective study; n=609 mother-infant pairs with follow-up at age 3–4 years	Gmean (SD) <ul style="list-style-type: none"> • Cord: 0.76 (1.7) • Child: 0.70 (1.7) 	FSIQ	Associations with PbB (β per 1 SD PbB): Cord PbB <ul style="list-style-type: none"> • Male: -2.65 (-4.66, -0.48) $p=0.04^*$ • Female: -0.18 (-1.63, 1.21) $p=0.83$ Child PbB <ul style="list-style-type: none"> • Male: -0.07 (-2.10, 2.17), $p=0.96$ • Female: 0.52 (-1.23, 2.40), $p=0.63$
Dietrich et al. 1986 Prospective study; n=280 mother-infant pairs	Prenatal (maternal): <ul style="list-style-type: none"> • Mean (SD): 8.0 (3.8) • Range: 1–27 Neonatal (age 10 days): <ul style="list-style-type: none"> • Mean (SD): 4.5 (2.9) • Range: 1–22 	MDI	Associations with maternal PbB (n=245), β per lnPbB (SE): -14.978 (6.114); $p < 0.02^*$ Associations with neonatal PbB (n=280), β per lnPbB (SE): -15.110 (5.083); $p < 0.003^*$ In males: F (1,122): 4.95; $p=0.03^*$
Dietrich et al. 1987 Prospective study; n=185 mother-infant pairs	Mean (SD, range): <ul style="list-style-type: none"> • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36) 	MDI PDI Motor maturity	β per lnPbB (SE): <ul style="list-style-type: none"> • 3-month: -12.113 (4.727); $p=0.01^*$ • 6-month: -2.117 (0.916); $p=0.02^*$ • β (SE): -13.248 (4.250); $p=0.002^*$ • β (SE): -0.570 (0.260); $p=0.03^*$

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Dietrich et al. 1989		MDI	
Prospective study; n=192 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3–4–47)		Structural Equation Model indicated associations (p≤0.05) between increasing prenatal PbB and 12-month MDI through decreasing birth weight. Standardized regression coefficients: • Prenatal PbB → birth weight: -0.15, p≤0.05* • Birth weight → 12-month MDI: 0.18, p≤0.05*
Dietrich et al. 1991		K-ABC scores	
Prospective study; n=258 4-year-old children	Mean (SD, range): (based on Dietrich et al. 1992) • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26)		Coefficients per µg/dL neonatal PbB: • Mental processing composite: -0.63; p<0.01* • Sequential processing: -0.68, p<0.01* • Simultaneous processing: -0.50; p<0.05* • Nonverbal: -0.63; p<0.01* • Achievement: -0.28; p<0.05*
Dietrich et al. 1992		FWS scores	
Prospective study; n=259 5-year-old children	Mean (SD, range): • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26) • Postnatal (5 years): 11.9 (6.4, 3–38)		Coefficients per µg/dL neonatal PbB: • FWS(T): -0.26 p<0.1* • FWS(L): -0.20, p<0.01* • FWS(R): -0.13, p<0.1* Coefficients per µg/dL concurrent PbB: • FWS(T): -0.11 p<0.1* • FWS(L): -0.06, p<0.1* • FWS(R): -0.08, p<0.05*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Dietrich et al. 1993a Prospective study; n=253 6–7-year-old children	Mean (SD): • Maternal: 8.3 (3.7) • Birth: 5 (3.4) • 4–5 years: 11.8 (6.3)	FSIQ	Adjusted β (SE) in IQ per each 1 µg/dL: • Prenatal: 0.15 (0.21), • Lifetime average: -0.13 (0.11); • Concurrent: -0.33 (0.14); p≤0.05*
Emory et al. 2003 Retrospective study; n=79 African-American mother-infant pairs	Mean (SD, 5 th –95 th percentile): • Maternal: 0.72 (0.86, 0.28–1.18)	FTII, Scaled Novelty Risk (risk of mental retardation later in life)	Score: PbB (SD): • Low risk: 0.65 µg/dL (0.80) • Medium risk: 0.89 µg/dL (0.88) • High risk: 1.01 µg/dL (0.126)
EPA 2014e (re-analysis of pooled cohort from Lanphear et al. 2005 with corrections to the database) Prospective; pooled-analysis; n=1,333 children (4.8–6 years of age) from seven prospective studies	Mean (95% CI): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each ln PbB (µg/dL) increase in PbB (95% CI): • 6–24 months: -2.21 (-3.38, -1.304)* • Lifetime average: -3.14 (-4.39, -1.88)* • Peak: -2.86 (-4.10, -1.61)* • Concurrent: -2.65 (-3.69, -1.61)* FSIQ change for concurrent PbB range: • 2.4–10 µg/dL: -3.8 points (-2.3, -5.3)* • 10–20 µg/dL: -1.8 points (-1.1, -2.6)* • 20–30 µg/dL: -1.1 (-0.7, -1.5)*
Evens et al. 2015 Population-based retrospective cohort study; n=47,168 children (third graders)	Mean (SD): 4.81 (2.22); Participants with PbB <10: 100%	ISAT reading scores	Regression coefficient (SE): -0.60 (0.03); p<0.0001* Adjusted RR: • 1 µg/dL: 1.06 (1.05, 1.07)* • 5 µg/dL: 1.32 (1.26, 1.39)*
		Math	Regression coefficient (SE): -0.50 (0.03); p<0.0001* Adjusted RR: • 1 µg/dL: 1.06 (1.05, 1.07)* • 5 µg/dL: 1.32 (1.26, 1.39)*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Geier et al. 2017 Cross-sectional study; n=1,411 children, age 6–15 years	Mean (SD): 1.32 (0.95) <P50: 0.2–1.007 P50–P75: 1.007–1.530 P75–P100: 1.530–13.50	Diagnosed with learning disability	OR per µg/dL: 1.19 (1.00, 1.40) p=0.044* OR for quartile relative to <50 th percentile (<P50): • P50–75: 1.46 (1.11, 1.92), p=0.0017* • P75–100: 1.95 (1.16, 3.29), p=0.0033*
Gomaa et al. 2002 Prospective study; n=197 children followed from birth to age 2 years	Umbilical cord mean (SD): 6.7 (3.4) Participants with PbB ≥10: 15.7%	MDI	β (SE): -4.48 (2.04); p=0.03*
Hong et al. 2015 Cross-sectional study; n=1,001 children (ages 8–11 years)	Gmean (GSD): 1.80 (1.40) IQ 5 th –95 th percentile range: 0.53–6.16	IQ	Regression coefficients per 10-fold increase in PbB: • Verbal IQ: -2.64 (-4.98, -0.30); p=0.027* • Full-scale IQ: -7.23 (-13.39, -1.07); p=0.021*
Hu et al. 2006 Prospective study; n=146 mother-child pairs	Mean±SD (range): • Umbilical cord: 6.20±3.88 (0.9–20.0) • Child 12-month: 5.22±3.41 (0.9–20.4) • Child 24-month: 4.79±3.71 (0.8–36.8) • Maternal 1 st trimester: 7.07±5.10 (1.49–43.6) • Maternal 2 nd trimester: 6.08±3.15 (1.58–22.4) • Maternal 3 rd trimester: 6.86±4.23 (1.53–33.1)	MDI	β per 1 SD change in ln PbB: • Umbilical cord: -0.35 (-4.72, 4.03); p=0.88 • Child 12-month: -2.38 (-6.24, 1.49); p=0.23 • Child 24-month: -1.00 (-3.93, 1.94); p=0.50 • Maternal 1st trimester: -4.13 (-8.10, -0.17); p=0.04* • Maternal 2 nd trimester: -4.08 (-8.29, 0.12); p=0.06 • Maternal 3 rd trimester: -2.42 (-6.38, 1.54); p=0.23

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^c
Jedrychowski et al. 2009			
	Umbilical cord PbB	MDI	β per lg cord PbB \pm SE:
Prospective study; n=444 children followed prenatally to age 3 years	<ul style="list-style-type: none"> Gmean: 1.29 Median: 1.23 Range: 0.44–6.90 		<ul style="list-style-type: none"> 12 months: -5.419 ± 2.935 ($-11.188, 0.3495$); $p=0.066$ 24 months: -7.653 ± 3.577 ($-14.684, -0.623$); $p=0.033^*$ 36 months: -6.717 ± 2.964 ($-12.546, -0.889$); $p=0.024^*$ All participants with PbB < 5 (combination of all testing times): -6.618 ± 2.499 ($-11.517, -1.719$); $p=0.008^*$
Jusko et al. 2008			
	Lifetime average:	FSIQ	
Prospective study; n=174 children recruited at age 24–30 months and evaluated for FSIQ at 6 years	<ul style="list-style-type: none"> Mean (SD): 7.2 (4.1) Range: 1.4–27.1 Participants < 10: 77% 		<ul style="list-style-type: none"> Associations between increasing PbB and decreasing FSIQ measured at age 6 years ($p=0.003$)[*] Comparison of children with PbB of 5–9.9 (high) to those with PbB < 5 (low) showed a 4.9-point decrease in FSIQ score (low: 91.3; high 86.4; $p=0.04$)[*] Adjusted changes in IQ for each 1 $\mu\text{g}/\text{dL}$ increase in peak lifetime PbB (p not reported): <ul style="list-style-type: none"> 2.1–10 $\mu\text{g}/\text{dL}$: -1.2 10–20 $\mu\text{g}/\text{dL}$: -0.32 20–30 $\mu\text{g}/\text{dL}$: -0.15
Kim et al. 2013b			
	Gmean (GSD):	MDI	β per 1 $\mu\text{g}/\text{dL}$ change in late pregnancy
Prospective birth cohort; n=884 mother infant pairs	Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5)		PbB: -1.94 ($-3.60, -0.29$); $p=0.02^*$

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Kordas et al. 2011	Mean (SD):	MDI (24 months)	<ul style="list-style-type: none"> β (SE) Cord PbB: -0.7 (0.3); $p < 0.05^*$ β (SE) Concurrent PbB: -0.1 (0.2)
Prospective study; n=186 children followed prenatally (to age 4 years)	<ul style="list-style-type: none"> Umbilical cord: 6.6 (3.3) 24 months: 8.1 (4.4) 48 months: 8.1 (3.6) 	PDI (24 months)	<ul style="list-style-type: none"> β (SE) Cord PbB: -0.4 (0.2) β (SE) Concurrent PbB: -0.2 (0.2)
		GCI (48 months)	<ul style="list-style-type: none"> β (SE) Cord PbB: -0.2 (0.3) β (SE) Concurrent PbB: -0.6 (0.2); $p < 0.05^*$
		Memory score	<ul style="list-style-type: none"> β (SE) Cord PbB: 0.1 (0.1) β (SE) Concurrent PbB: -0.3 (0.1)
Lanphear et al. 2000a	Gmean: 1.9	Arithmetic	Regression coefficients (SE):
Cross-sectional study;	Participants with PbB		<ul style="list-style-type: none"> PbB < 2.5: -1.28 (0.98); $p = 0.20$ PbB < 5.0: -1.06 (0.48); $p = 0.03^*$ PbB < 7.5: -1.06 (0.39); $p = 0.01^*$ PbB < 10: -0.89 (0.32); $p = 0.008^*$
n=4,853 children (ages 6–16 years)	<ul style="list-style-type: none"> ≥ 5: 9.7% ≥ 10: 2.1% 	Reading	Regression coefficients (SE):
			<ul style="list-style-type: none"> PbB < 2.5: -1.71 (0.93); $p = 0.07$ PbB < 5.0: -1.66 (0.36); $p < 0.001^*$ PbB < 7.5: -1.53 (0.31); $p < 0.001^*$ PbB < 10: -1.44 (0.30); $p < 0.001^*$
		Block design	Regression coefficients (SE):
			<ul style="list-style-type: none"> PbB < 2.5: -0.08 (0.22); $p = 0.72$ PbB < 5.0: -0.05 (0.07); $p = 0.45$ PbB < 7.5: -0.11 (0.06); $p = 0.04^*$ PbB < 10: -0.13 (0.06); $p = 0.03^*$
		Digit span	Regression coefficients (SE):
			<ul style="list-style-type: none"> PbB < 2.5: -0.25 (0.17); $p = 0.17$ PbB < 5.0: -0.09 (0.07); $p = 0.20$ PbB < 7.5: -0.09 (0.05); $p = 0.11$ PbB < 10: -0.08 (0.04); $p = 0.03^*$

2. HEALTH EFFECTS

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Lanphear et al. 2005 (same cohorts used for Budtz-Jorgensen et al. 2013)	Mean (96% CL): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each ln PbB (µg/dL) increase in PbB: • 6–24 months: -2.04 (-3.27, -0.81)* • Lifetime average: -3.04 (-4.33, -1.75) • Peak: -2.85 (-4.10, -1.60)* • Concurrent: -2.70 (-3.74, -1.66)*
Prospective; pooled-analysis; n=1,333 children (4.8–6 years of age) from seven prospective studies			FSIQ change for lifetime average PbB: • 2.4–10 µg/dL: -3.9 points (-2.4, -5.3)* • 10–20 µg/dL: -1.9 points (-1.2, -2.6)* • 20–30 µg/dL: -1.1 (-0.7, -1.5)*
Lanphear et al. 2019 (re-analysis of data reported in Lanphear et al. 2005; same cohorts used for Budtz-Jorgensen et al. 2013)	Median (96% CL): • Lifetime average: 11.9 (3.6, 34.5) • Peak: 18.0 (6.2, 47.0) Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each ln PbB (µg/dL) increase in PbB: • 6–24 months: -2.21 (-3.38, -1.04)* • Peak: -2.86 (-4.10, -1.61)* • Lifetime average: -3.25 (-4.51, -1.99)* • Concurrent: -2.65 (-3.69, -1.61)*
Prospective; pooled-analysis; n=1,333 children (4.8–6 years of age) from seven prospective studies			FSIQ change for concurrent PbB: • 2.4–10 µg/dL: -3.8 points (-2.3, -5.3)* • 10–20 µg/dL: -1.8 points (-1.1, -2.6)* • 20–30 µg/dL: -1.1 (-0.7, -1.5)*
Lin et al. 2013 Prospective (Taiwan Birth Panel Study; birth dates: April 2004–January 2005) of 230 mother-infant pairs from Taipei, Taiwan, followed until age 2 years	Umbilical cord • Mean (SD): 1.30 (0.75) • Range: 0.016–4.32	Cognitive score	Regression analysis comparing PbB ≥1.645 (75 th percentile) and PbB <1.645. Adjusted β (SE): • Total score: -4.23 (1.82); p<0.05* • Cognitive: -5.35 (2.19); p<0.05* • Language: -2.53 (1.89); p≥0.05

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Liu et al. 2014b Prospective study; n=243 infants followed from birth to age 3 years	Umbilical cord (mean±SD): • Low PbB group: 1.35±0.26 • High PbB group: 5.63±0.32	MDI	Regression coefficients: • 6 months: -1.647 (-2.094, -1.200); p=0.016* • 12 months: -1.458 (-1.832, -1.084); p=0.023* • 24 months: -1.385 (-1.683, -1.087) p=0.033* • 36 months: -1.291 (-1.550, -1.032); p=0.036* Increasing PbB at ages 24 and 36 months was associated with decreasing MDI scores measured at 24 and 36 months, respectively; β: • 24 months: -1.403; p=0.026* • 36 months: -1.298; p=0.036*
PDI			
Mazumdar et al. 2011 A prospective of 43 adults followed from birth (1979–1981) to age 28–30 years	Mean (SD): • Cord: 6.5 (5.3) • 6 months: 8.0 (5.3) • 12 months: 10.0 (6.7) • Age 2 years: 7.7 (4.0) • Age 4 years: 6.7 (3.6) • Age 10 years: 3.0 (2.7)	FSIQ	Regression coefficients at 36 months: -1.302 (-1.572, -1.031); p=0.041* Change in FSIQ per 1 µg/dL increase in PbB. β for average late childhood PbB (mean of 4- and 10-year PbB): • Unadjusted: -1.89 (-3.30, -0.47), p<0.01* • Adjusted for maternal IQ: -1.11 (-2.29, 0.06) • Other adjustments: 95% UCLs <0
McLaine et al. 2013 Population-based retrospective cohort study; n=3,406 children (kindergarteners)	Median: 4.2 Interquartile range: 2.6, 6.0	PALS-K scores	Mean differences (95% CI) in PALS-K scores (85% CL), compared to PbB <5: • PbB 5–9: -4.51 (-6.61, -2.85); p>0.182 • PbB ≥10: -10.13 (-13.30, -6.96); p>0.182 PR for falling below the PALS-K benchmark, compared to PbB <4: • PbB 5–9: 1.21 (1.19, 1.23); p<0.001* • PbB ≥10: 1.56 (1.51, 1.60); p<0.001*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Min et al. 2009 Prospective study; n=267 children followed prenatally age 11 years	Mean (SD): • 4 years: 7.0 µg/dL (4.1)	FSIQ	Regression coefficient (SE): • 4 years: -0.50 (0.20), p<0.05* • 9 years: -0.41 (0.19), p<0.05* • 11 years: -0.54 (0.19); p<0.01*
Miranda et al. 2009 Population-based retrospective cohort study; n=57,678 4 th grade children	Mean: 4.8 Median: 4 Range: 1–16	EOG scores	Multivariate regression coefficients for PbB (µg/dL) of: • PbB 2: -0.30 (-0.58, -0.01); p<0.0001* • PbB 3: -0.46 (-0.73, -0.19); p<0.0001* • PbB 4: -0.52 (-0.79, -0.24); p<0.0001* • PbB 5: -0.80 (-1.08, -0.51); p<0.0001* • PbB 6: -0.99 (-1.29, -0.68); p<0.0001* • PbB 7: -1.07 (-1.40, -0.74); p<0.0001* • PbB 8: -1.35 (-1.73, -0.97); p<0.0001* • PbB 9: -1.20 (-1.64, -0.75); p<0.0001* • PbB ≥10: -1.75 (-2.09, -1.41); p<0.0001*
Polanska et al. 2018 Prospective study; n=538 mother-child pairs with follow-up of 303 children at age 2 years	Gmean (SD) (range) • 2 nd trimester: 0.99 (0.15) (0.29, 2.63) • Cord: 0.96 (0.16) (0.24, 5.65)	BSID III	β score per µg/dL cord In PbB: Cognitive score: • Females: 0.34 (-1.30, 1.98), p=0.68 • Males: -2.07 (-4.07, -0.06), p=0.04* Language score: • Females: -0.29 (-2.23, 1.65), p=0.77 • Males: -0.43 (-2.81, 1.95), p=0.72
Rodrigues et al. 2016 Prospective study; n=812 mother-child pairs with follow-up of 5251, children at age 2–3 years	Median (P24, P75, maximum) • Sirajdikhan: 7.6 (5.5, 10.4) • Pabna: <LOD (<LOD, 3.8, 13.8)	BSID III	β score per µg/L child PbB: Cognitive score: • Sirajdikhan: -0.17 (0.09), p=0.05* • Pabna: 0.02 (0.12), p=0.87

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Rooney et al. 2018 Longitudinal study; n=330 children with follow-up at age 12 and 17 years	Mean (SD) at age 8–12 years <ul style="list-style-type: none"> Females: 4.42 (2.19) Males: 5.26 (2.73) 	Learning, memory, and executive function test	Genetic variants of N-methyl-D-aspartate receptors (NMDAR subunits GRIN2A and GRIN2B) were effect modifiers on associations between increasing PbB (at age 8–12 years) and decreasing performance on learning and memory and executive functions
Ruebner et al. 2019 Cross-sectional study; n=412 children (median age 15.4 years) from prospective study of CKD in children	Median (P24, P75): 1.2 (0.8, 1.8)	FSIQ, CPT	β score per µg/dL (95% CI): FSIQ: <ul style="list-style-type: none"> PbB: -2.1 (-3.9, -0.2), p=0.029*CPT variability score: PbB: 1.8 (0.2, 3.5), p=0.033*
Schnaas et al. 2006 Prospective study; n=150 followed from birth to age 10 years	Maternal during full pregnancy <ul style="list-style-type: none"> Gmean (range): 8.0 (1–33) Maternal PbB during pregnancy weeks 28–36 <ul style="list-style-type: none"> Gmean (95% CI): 7.3 (1.5–17.4) Child 1–5 years <ul style="list-style-type: none"> Gmean (range): 9.8 (2.8–36.4) Child 6–10 years <ul style="list-style-type: none"> Gmean (range): 6.2 (2.2–18.6) 	FSIQ	β assessed at age 6–10 years: <ul style="list-style-type: none"> Ln maternal PbB (28 weeks pregnancy): -4.00 (-6.37, -1.65); p=0.001* Ln child PbB (6–10 years): -2.45 (-4.09, -0.81); p=0.003*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Shadbegian et al. 2019			
Retrospective study; n=560,624 children with PbB measured at ages 0–5 years and cognitive assessments during school grades 3–8	Mean (SD) Whole cohort <ul style="list-style-type: none"> • <10 µg/dL: 3.66 (1.90) • ≤5 µg/dL: 2.89 (1.18) CEM stratum ≤5 µg/dL: 2.40 (1.24)	Standardized academic achievement tests	Percentile score change relative to ≤1 µg/dL CEM stratum (SE) for children who had geometric mean PbB >1 and ≤5 µg/dL: Math percentile for PbB strata: <ul style="list-style-type: none"> • 2 µg/dL: -0.38 (0.19), p>0.05 • 3 µg/dL: -0.56 (0.20), p<0.01* • 4 µg/dL: -0.96 (0.23), p<0.001* • 5 µg/dL: -0.51(0.30), p>0.05 Reading percentile for PbB strata: <ul style="list-style-type: none"> • 2 µg/dL: -0.55 (0.19), p<0.01* • 3 µg/dL: -1.02 (0.20), p<0.001* • 4 µg/dL: -1.31 (0.23), p<0.001* • 5 µg/dL: -0.97 (0.30), p>0.001*
Sobin et al. 2015			
Cross-sectional study; n=252 children (age 5.1–11.8 years)	Mean (SD): <ul style="list-style-type: none"> • Females: 2.7 (1.5) • Males: 2.4 (1.0) • 96% <5.0 µg/dL 	Working memory	β (SE): 0.11 (0.03), p<0.01*
Taylor et al. 2017			
Prospective study; n=14,062 mother- infant pairs with follow-up of 404 children at age 4 years and n=2,217 children at age 8 years	Mean (SD): <ul style="list-style-type: none"> • Maternal (11 weeks): 3.67 (1.46) • Child (30 months): 4.22 (3.12) 	FSIQ	β for score per µg/dL at age 8 years: Females: <ul style="list-style-type: none"> • Verbal: 0.71 (0.11, 1.32), p=0.021* • Performance: 0.57 (-0.11, 1.24), p=0.099 • Total: 0.73 (0.13, 1.33), p=0.017 Males: <ul style="list-style-type: none"> • Verbal: -0.15 (-0.90, 0.60), p=0.72 • Performance: -0.42 (-1.19, 0.35), p=0.29 • Total: -0.29 (-1.02, 0.44), p=0.44

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Tellez-Rojo et al. 2006	Mean (SD):	MDI	β per ln PbB 12 months:
Prospective study; n=294 children followed from birth to age 2 years	<ul style="list-style-type: none"> Cord: 4.85 (3.0) 12 months: 4.27 (2.14) 24 months: 4.28 (2.25) 		<ul style="list-style-type: none"> <10 $\mu\text{g/dL}$: -0.15, $p=0.57$ ≥ 10 $\mu\text{g/dL}$: -0.71, $p=0.17$ β per lnPbB 24 months: <ul style="list-style-type: none"> <10 $\mu\text{g/dL}$: -1.04, $p<0.01^*$ ≥ 10 $\mu\text{g/dL}$: 0.07, $p=0.84$
Vigeh et al. 2014	Mean \pm SD (range):	ECDI score	OR 1 st trimester: 1.74 (1.18–2.57); $p=0.005^*$
Prospective study; n=174 mother-child pairs, birth to 36 months	<ul style="list-style-type: none"> 1st trimester: 4.15\pm2.43 (1.6–20.5) 2nd trimester: 3.44\pm1.28 (1.1–7.5) 3rd trimester: 3.78\pm1.40 (1.5–8.0) Umbilical cord: 2.86\pm1.09 (1.2–6.9) 		
Wasserman et al. 1994, 1997, 2003	Mean (SD):	FSIQ	β (SE) for each ln PbB increase:
Prospective study; n=332 children age 4 years, 261 children age 7 years, 167 children age 10–12 years	<ul style="list-style-type: none"> Age 4 years: 9.6, Pristina Age 10–12 years: 6.1 (1.9), Pristina 30.9 (9.6), K. Mitrovica 		<ul style="list-style-type: none"> 4 years: -9.43 (2.44); $p=0.000^*$ Lifetime AUC 7 years: -8.59 (1.89); $p<0.05^*$ Lifetime average 10–12 years: -5.31 (1.98); $p<0.05^*$
Zhang et al. 2013	Mean (SD): 7.12 (7.26)	Math	<ul style="list-style-type: none"> OR 1–5 PbB ($\mu\text{g/dL}$): 1.42 (1.24, 1.63)* OR 6–10 PbB ($\mu\text{g/dL}$): 2.00 (1.74, 2.30)* OR >10 PbB ($\mu\text{g/dL}$): 2.40 (2.07, 2.77)*
Population-based retrospective cohort study; n=8,831, 7,708, and 4,742 students in grades 3, 5, and 8, respectively	Analysis: academic achievement	Science	<ul style="list-style-type: none"> OR 1–5 PbB ($\mu\text{g/dL}$): 1.33 (1.10, 1.62)* OR 6–10 PbB ($\mu\text{g/dL}$): 2.22 (1.82, 2.72)* OR >10 PbB ($\mu\text{g/dL}$): 2.26 (1.84, 2.78)*
		Reading	<ul style="list-style-type: none"> OR 1–5 PbB ($\mu\text{g/dL}$): 1.45 (1.27, 1.67)* OR 6–10 PbB ($\mu\text{g/dL}$): 2.21 (1.92, 2.55)* OR >10 PbB ($\mu\text{g/dL}$): 2.69 (2.31, 3.12)*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Zhou et al. 2017 Prospective study; n=139 mother-infant pairs followed from birth to 24–36 months	Gmean (95% CI) Mid-late pregnancy: 3.30 (3.05, 3.57)	Gesell Development Scale, prenatal stress Global Severity Index	β for development quotient per µg/dL: All children: <ul style="list-style-type: none"> Adaptive behavior: 3.60 (-3.64, 10.83) Language: -6.76 (-17.29, 3.77) Social behavior: -6.45 (-15.55, 2.65)
Children from mothers who exhibited high prenatal stress:			
<ul style="list-style-type: none"> Adaptive behavior: -17.93 (-35.83, -0.03)* Language: -33.82 (-60.04, -7.59)* Social behavior: -41.00 (-63.11 -18.89)* 			
Mood and behavior			
Arbuckle et al. 2016 Cross-sectional study; n=2,097 children aged 6–19 years	Gmean (95% CI) age 6–11 years: 0.91 (0.81, 0.99) age 12–19 years: 0.80 (0.74, 0.85)	ADD/ADHD	ORs for ln(PbB): <ul style="list-style-type: none"> ADD/ADHD: 2.39 (1.32, 4.32)* Emotional symptoms: 1.08 (0.68, 1.71) Hyperactivity/inattention: 2.33 (1.59, 3.43)* Total difficulties: 2.16 (1.33, 3.51)*
Boucher et al. 2012 Prospective study; n=272 children (mean age 11.3 years)	Mean±SD (range): <ul style="list-style-type: none"> Umbilical cord: 4.7±3.3 (0.8–20.9) Current: 2.7±2.2 (0.4–12.8) 	ADHD-inattentive type ADHD-hyperactive-impulsive type ODD and/or CD	Adjusted ORs: <ul style="list-style-type: none"> T2 (n=94): 1.06 (0.42, 2.66) T3 (n=91): 1.01 (0.38, 2.64) T2(n=94): 4.01 (1.06, 15.23)* T3(n=91): 5.52 (1.38, 22.12)* T2 (n=94): 1.90 (0.88, 4.11) T3 (n=91): 1.53 (0.67, 3.49)
Behavior problem scores			Umbilical cord PbB was not associated with associated with behavior problem scores (data not reported).

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Braun et al. 2006 Cross-sectional study; n=4,704 children (ages 4–15 years)	Quintiles: • Q1 (reference): ND–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.3 • Q4: 1.4–2.0 • Q5: ≥2.0	ADHD	Adjusted ORs: • Q2: 1.1 (0.4, 3.4); p=0.804 • Q3: 2.1 (0.7, 6.8); p=0.195 • Q4: 2.7 (0.9, 8.4); p=0.086 • Q5: 4.1 (1.2, 14.0); p=0.026* • p-trend: 0.012*
Braun et al. 2008 Cross-sectional study; n=3,082 children (ages 8–15 years)	Quartiles: • Q1 (reference): 0.2–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.4 • Q4: >2.0	Conduct disorder	Adjusted ORs: • Q2: 7.24 (1.06, 49.47)* • Q3: 12.37 (2.37, 64.56*) • Q4: 8.64 (1.87, 40.04)*
Choi et al. 2016 Longitudinal study; n=2,159 children (ages 7–9 years)	Gmean (GSD): • All participants >7 years: 1.62 (1.52) • Boys: 1.65 (1.75) • Girls: 1.47 (1.76); p<0.001, compared to boys	ADHD	• RR for PbB ≥2.17 (compared to PbB <2.17): 1.552 (1.002, 2.403)*
Desrochers-Couture et al. 2019 Longitudinal study; n=212 Inuit children followed from birth and evaluated at mean age 11.4 and 18.5 years	Gmean (GSD) • Cord: 3.80 (1.84) • Child: 2.34 (1.86) • Adolescent: 1.63 (2.00)	ADHD	β per log ₂ µg/dL PbB: Child: • Externalizing: 0.61 (-0.63, 1.96) • Hyperactivity-impulsivity: 0.11 (-0.14, 0.37) • Oppositional defiant/conduct disorder: 0.02 (-0.20, 0.21) Adolescent: • Externalizing interacting with child externalizing: 0.32 (0.08, 0.72)*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Dietrich et al. 2001 Prospective study; n=195 subjects (age 15–17 years)	Categories: Lowest: <10 Low: 10–15 Medium: 16–20 High: >20	SRDBS scores	β (SE): <ul style="list-style-type: none"> • Prenatal PbB: 0.192 (0.076); p=0.002* • 78-month PbB: 0.193 (0.061); p=0.002* • Average child PbB: 0.101 (0.047); p=0.036*
Froehlich et al. 2009 Cross-sectional study; n=2,588 children (ages 8–15 years)	Tertiles T1: 0.2–0.8 T2: 0.9–1.3 T3: >1.3	ADHD	Adjusted ORs: <ul style="list-style-type: none"> • T2: 1.7 (0.97, 2.9); p=0.06 • T3: 2.3 (1.5, 3.8); p=0.001*
Fruh et al. 2019 Prospective study; n=1,006 mother-child pairs with follow-up at age 8 years; Massachusetts	Erythrocyte Pb: Median: 1.1 25 th –75 th % range: 0.6	BRIEF and SDQ	β for change in score for an IQR increase in maternal 2 nd trimester erythrocyte Pb: Parent-rated SDQ: <ul style="list-style-type: none"> • Total difficulties: 0.36 (-0.04, 0.77) • Emotional problems: 0.18 (0.03, 0.33)*
		Parent-rated BRIEF score:	<ul style="list-style-type: none"> • Behavioral regulation index: 0.69 (-0.13, 1.51) • General executive composite: 0.73 (-0.06, 1.52) • Plan organize: 0.85 (0.12, 1.59)*
Geier et al. 2018 Cross-sectional study; n=2,109 children, age 10–19 years	Mean (SD): 1.16 (1.27) Quartiles, range: <ul style="list-style-type: none"> • 0–50th: 0.2–0.88 • 50th–75th: 0.88–1.26 • 75th–100th: 1.26–34.8 	ADD	OR for diagnosis of ADD: Total sample (per µg/dL): 1.292 (1.025, 1.545) p=0.0301* Upper quartile PbB relative to 0–50 th percentile as reference: <ul style="list-style-type: none"> • 50–75th %: 1.28 (0.82, 2.00), p=0.2466* • 75–100th %: 1.59 (1.05, 2.39), p=0.0130*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
He et al. 2019 Meta-analysis of seven studies of associations between PbB and risk of ADHD diagnosis	Range of study means: 0.73, 8.77	ADHD	Mean risk difference (95% CI): <ul style="list-style-type: none"> All studies (7): 0.59 (0.50, 0.68), p<0.0001* PbB <3 µg/dL: 0.47 (0.39, 0.56), p<0.0001* Age 5–12 years compared to age >12 years: 1.35 (0.28, 2.41), p<0.0001*
Hong et al. 2015 A cross-sectional study; n=1,001 children (age 8–11 years)	Gmean (GSD): 1.80 (1.40) Range: 0.53–6.16	ADHD-hyperactive-impulsive type ADHD-inattentive type Total score	PbB (log-transformed) OR: 3.66 (1.18, 6.13); p=0.004* <ul style="list-style-type: none"> OR: 2.72 (-0.12, 5.56); p=0.060 OR: 6.38 (1.36, 11.40); p=0.013*
Huang et al. 2016 Prospective study of mother-infant pairs with follow-up of 578 children at age 6–13 years	Mean (SD): 3.4 (3.1)	ADHD	β per 1 µg/dL: <ul style="list-style-type: none"> Hyperactivity: 1.2 (0.3, 2.0), p=0.01* Restless-impulsive: 1.2 (0.3, 2.0), p=0.007* Hyperactive-impulsive: 1.1 (0.2, 2.0), p=0.02*
Ji et al. 2018 Prospective study of mother-infant pairs recruited beginning 1998 with follow-up of 1,479 children at median age 9.6 years	Mean (SD): 2.2 (1.6) <ul style="list-style-type: none"> All: 2.2 (1.6) ADHD: 2.4 (1.9) No neuro-developmental disorder: 2.1 (1.5) 	ADHD	OR for ADHD diagnosis. Males and females: OR per ln PbB (µg/dL): 1.25 (1.01, 1.56) p=0.045* OR relative to <2 µg/dL reference: <ul style="list-style-type: none"> 2–4 µg/dL: 1.08 (0.81, 1.44) p=0.622 5–10 µg/dL: 1.73 (1.09, 2.73) p=0.019* OR relative to <5 µg/dL reference: <ul style="list-style-type: none"> 5–10 µg/dL: 1.66 (1.08, 2.56) p=0.020* Males: OR 5–10 µg/dL relative to <5 µg/dL reference: <ul style="list-style-type: none"> Males: 2.49 (1.46, 4.26) p=0.001* Females: 0.68 (0.27, 1.69) p=0.401

2. HEALTH EFFECTS

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Joint effects of sex and PbB: OR 5–10 $\mu\text{g/dL}$ relative to <5 $\mu\text{g/dL}$ reference:			
<ul style="list-style-type: none"> • Males: 7.48 (4.29, 13.02) $p < 0.001$* • Females 0.69 (0.28, 1.71) $p = 0.426$ 			
OR for ADHD diagnosis; OR per $\mu\text{g/dL}$:			
<ul style="list-style-type: none"> • All ADHD: 1.28 (0.89, 1.83) • Inattention: 1.63 (1.03, 2.58), $p < 0.05$* • Hyperactivity/impulsivity: 1.04 (0.53, 2.07) 			
Joo et al. 2017	Gmean (SD): Cases: 1.65 (1.45) Controls: 1.49 (1.48)		
Case-control study; n=214 child ADHD cases and 214 controls, age 6–10 years			
Joo et al. 2018	Gmean (SD): Early pregnancy: 1.28 (1.48) Late pregnancy: 1.24 (1.57) Cord: 0.90 (1.57) 2 years: 1.55 (1.49) 3 years: 1.43 (1.44) 5 years: 1.29 (1.38)	Behavioral problems (Child Behavior Checklist)	β for score per $\mu\text{g/dL}$: PbB at age 2 years: <ul style="list-style-type: none"> • Females: 3.82 (1.25, 3.69)* • Males: 0.22 (-1.87, 2.32) PbB at age 3 years: <ul style="list-style-type: none"> • Females: 2.43 (-1.00, 5.87) • Males: 0.48 (-2.17, 3.12) PbB at age 5 years: <ul style="list-style-type: none"> • Females: 5.72 (0.44, 10.99)* • Males: 1.37 (-2.06, 4.80)
Kim et al. 2016	Mean (95% CI): <ul style="list-style-type: none"> • Ages 7–8 years: 1.64 (1.60, 1.68) • Ages 9–10 years: 1.58 (1.55, 1.61) • Ages 11–12 years: 1.58 (1.55, 1.61) 	ASSQ SRS	PbB (log transformed) β (SE): <ul style="list-style-type: none"> • 7–8 years: 0.151 (0.061, 0.242)* • 9–10 years: -0.023 (-0.143, 0.097) • 11–12 years: 0.054 (-0.061, 0.170) <ul style="list-style-type: none"> • PbB at 7–8 years: 2.489 (1.378, 3.600)* • PbB at 9–10 years: 1.295 (-0.235, 2.825) • PbB at 11–12 years: β (SE): 0.724 (-0.727, 2.176)
Prospective study; n=2,473 children (age 7–8 years)			

2. HEALTH EFFECTS

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Liu et al. 2014a			
Prospective study; n=332 mother-infant pairs	Mean (SD): <ul style="list-style-type: none">Low PbB group<ul style="list-style-type: none">1st trimester: 1.22 (0.28)2nd trimester: 1.01 (0.19)3rd trimester: 1.19 (0.23)Delivery: 1.26 (0.25)High PbB group<ul style="list-style-type: none">1st trimester: 6.49 (0.62)2nd trimester: 5.63 (0.43)3rd trimester: 6.31 (0.51)Delivery: 6.65 (0.55)	NBNA score	β : <ul style="list-style-type: none">1st trimester: -4.86 (-8.831, -0.889); p=0.03*2nd trimester: -3.98 (-8.180, 0.220); p=0.07*3rd trimester: -3.65 (-6.609, 1.309); p=0.21Delivery: -3.39 (-7.531, 0.751); p=0.11
Liu et al. 2015b	Mean (SD): 6.26 (2.54)	Sleep onset delay	β : 0.033 (0.009, 0.056); p=0.006*
Prospective study; n=665 children (ages 3–13 years)			
Park et al. 2016	Gmean \pm SD (range): Cases: 1.90 \pm 0.86 (0.37, 5.35) Controls 1.59 \pm 0.68 (0.18, 3.41) Q1: 0.18, 1.12 Q2: 1.13, 1.71 Q3: 1.72, 2.29 Q4: 2.30, 5.35	ADHD	OR for ADHD diagnosis: All subjects: 1.60 (1.04, 2.25), p=0.03* Relative to Q1: Q2: 1.26 (0.56, 2.84), p=0.39 Q3: 1.26 (0.55, 2.87), p=0.61 Q4: 2.54 (1.09, 5.94), p=0.03*
Case-control study of child (mean age 9 years) ADHD cases (n=114) and controls (n=114)			

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Sioen et al. 2013 Prospective study; n=270 children, followed newborn to 8 years	Umbilical cord mean (25 th –75 th percentiles): 1.43 (0.73–2.53)	Hyperactivity	OR: 2.940 (1.172, 7.380); p=0.022*
Stroustrup et al. 2016 Prospective study, n=948 mother-infant pairs with follow-up of 500 children at age 24 months	Median (IQR): 2 nd trimester: 2.8 (2.7)	Temperament (TTS=easy, intermediate, or difficult); maternal postnatal depression (EPDS)	OR (95% CI) corresponding to a 1 unit change in ln(maternal PbB $\mu\text{g/dL}$) for TTS score, easy score as reference: <ul style="list-style-type: none"> Intermediate: 0.88 (0.59, 1.3) Difficult: 1.52 (1.03, 2.26)* Probability of demonstrating difficult TTS score was approximately doubled if EPDS score was high
Wang et al. 2008 Case-control study; n=630 children (ages 4–12 years)	Means (SE): <ul style="list-style-type: none"> ADHD cases: 8.77 (3.89) Controls: 5.76 (3.36) Cases versus control: p<0.05 Tertiles: <ul style="list-style-type: none"> T1 (reference): ≤ 5 T2: 5–10 T3: ≥ 10 	ADHD	OR: <ul style="list-style-type: none"> T2: 4.92 (3.47, 6.98); p<0.01* T3: 6.00 (4.11, 8.77); p<0.01*
Winter and Sampson 2017 Prospective study of birth cohort (n=1,255) with follow-up from birth to age 18 years (n=208)	Means (SD) at age <6 years: 6.14 (4.58)	Impulsivity, anxiety, or depression (Child Behavior Checklist)	β for score per $\mu\text{g/dL}$: <ul style="list-style-type: none"> Impulsivity: 0.08 (0.01, 0.16)* Anxiety or depression: 0.11 (0.01, 0.21)*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^c
Neuromotor neurosensory function			
Chiodo et al. 2004	Mean (SD, range): 5.4 (3.3, 1–25)	Battery test performance	Tests with declines (β) at <3 , <5 , <7.5 , or <10 $\mu\text{g}/\text{dL}$: <ul style="list-style-type: none"> • Block design: <10, <5; $p \leq 0.05^*$ • Digit span backwards: <7.5; $p \leq 0.05^*$ • Beery visual-motor integration: <10, <5; $p \leq 0.05^*$ • MFF (number correct): <5; $p \leq 0.05^*$ • Attention-TRF: <3; $p \leq 0.05^*$ • Barkley-inattention: <5 <3; $p \leq 0.05^*$ • Withdrawn-TRF: <7.5, <3; $p \leq 0.05^*$ • Barkley off-task: <10, <5; $p \leq 0.05^*$ • Sternberg RT “Yes: <5, <3; $p \leq 0.05^*$ • Color naming: <5; $p \leq 0.05^*$ • CPT visual (number correct): none • Seashore rhythm: <3; $p \leq 0.05^*$ • Mental rotation RT “forward”: <10, <7.5; $p \leq 0.05^*$
Prospective study; n=237 children (age 7.5 years)			
Dietrich et al. 1987	Mean (SD, range):	Motor maturity	Associations with 3-month In PbB, β (SE): <ul style="list-style-type: none"> • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36)
Prospective study; n=185 mother-infant pairs		PDI	Associations with 3-month In PbB, β (SE): <ul style="list-style-type: none"> • PDI: -13.248 (4.250); $p=0.002^*$ • Motor maturity: -0.570 (0.260); $p=0.03^*$ Associations with 6-month In PbB, β (SE): <ul style="list-style-type: none"> • PDI: -2.117 (0.916); $p=0.02^*$ • Motor maturity: -0.092 (0.056); $p=0.11$ Associations with 3-month In PbB, β (SE): <ul style="list-style-type: none"> • PDI: -13.248 (4.250); $p=0.002^*$ • Associations with 6-month In PbB, β (SE): PDI: -2.117 (0.916); $p=0.02^*$

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Dietrich et al. 1989		PDI	β (SE), 12 months: -14.09 (7.26); p=0.054
Prospective study; n=192 mother-infant pairs	Mean (SD, range): <ul style="list-style-type: none">• Prenatal (maternal): 8.2 (3.6, 1–27)• Neonatal (10 days): 4.8 (3.1, 1–23)• Neonatal (3 months): 6.0 (3.5, 1–20)• Neonatal (6 months): 7.9 (4.8, 1–35)• Neonatal (9 months): 11.5 (6.9, 2–57)• Neonatal (12 months): 14.2 (7.3–4–47)	SEM indicated associations between increasing prenatal PbB and race and 12-month PDI. <ul style="list-style-type: none">• Prenatal PbB --> 12-month PDI: -0.47, p≤0.05*• Prenatal PbB x race --> birth weight: 0.97, p≤0.05*• Race --> 12-month MDI: -0.72, p≤0.05*	
Dietrich et al. 1993b		Motor performance	Tests with (p≤0.05) declines (β) associated with neonatal (N), mean lifetime (L) or concurrent (C) PbB: <ul style="list-style-type: none">• Bilateral coordination: N, M• Visual motor control: C• Upper limb speed and dexterity: C, M, N• Fine motor composite: C, M, N
Prospective study; n=245 children (age 6 years)	Mean (SD): <ul style="list-style-type: none">• Prenatal (maternal): 8.4 (3.8)• Neonatal: 4.8 (3.1)• Life average• 6 years: 10.1 (5.6)• Lifetime average quartile range: 7–22		
Ethier et al. 2012		Delay of N150 latency of VEP	Association between increasing cord PbB and delay of N150 latency of VEP at multiple contracts. Mean latency (estimated from reported bar plot): <ul style="list-style-type: none">• ≥4.15 µg/dL: ~160 ms, p<0.05*• <4.15 µg/dL: ~153 ms (reference)
Prospective longitudinal, n=149 children (age 10–13 years)	Mean (SD, range): <ul style="list-style-type: none">• Cord: 4.6 (3.1, 0.8–19.5)• 11 years: 2.6 (2.3, 0.4–12.8)		
Fraser et al. 2006		Hand movements	β -0.30, p≤0.01*
Prospective study; n=101 children (age 5 years)	Mean (SD): Cord: 4.9 (3.7) Child: 5.3 (4.9)	Sway velocity	β -0.28, p≤0.01*
		Transversal sway	β 0.24, p≤0.05*

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Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Kim et al. 2013b Prospective birth cohort, n=884 mother infant pairs	Gmean (GSD): Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5)	PDI	β per 1 µg/dL change in PbB: -1.69 (-3.65, -0.27); p=0.09
Liu et al. 2018b Cross-sectional study; n=234 children, age 3–7 years	Median (SE) e-waste location: 4.94 (0.20) reference location: 3.85 (1.81)	Hearing (pure tone conduction >25 dB)	OR for hearing loss per µg/dL (95% CI): • Hearing loss 1.24 (1.029, 1.486) p<0.05* • Low frequency loss: 1.02 (0.869, 1.190) • High frequency: 1.08 (0.839, 1.379)
Osman et al. 1999 Retrospective study; n=155 children (age 4–14 years)	Median (range): • 7.2 (1.9–28.1)	Hearing threshold	β per 1 change in PbB for right ear for full cohort: • 0.5 kHz: 0.054 (0.035, 0.074)* • 1 kHz: 0.044 9 (0.026, 0.062)* • 2 kHz: 0.048 (0.029, 0.066)* • 4 kHz: 0.060 (0.039, 0.081)* • 6 kHz: 0.068 (0.044, 0.092)* • 8kHz: 0.072 (0.050, 0.094)* β per 1 change in PbB for left ear: • 0.5 kHz: 0.051 (0.026, 0.075)* • 1 kHz: 0.032 (0.014, 0.050)* • 2 kHz: 0.036 (0.019, 0.053)* • 4 kHz: 0.039 (0.020, 0.059)* • 6 kHz: 0.004 (0.044, 0.049)* • 8kHz: 0.047 (0.024, 0.080)*
Association (p<0.05) between increasing PbB and increasing hearing threshold at all frequencies in PbB stratum <10 µg/dL (thresholds not reported)*			

2. HEALTH EFFECTS

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Polanska et al. 2018 Prospective study; n=539 mother-child pairs with follow-up of children at age 2 years; 280 blood samples and 303 cord blood samples were randomly chosen for analysis	Gmean (SD) (range) • 2 nd trimester: 0.99 (0.15) (0.29, 2.63) • Cord: 0.96 (0.16) (0.24, 5.65)	BSID III	β score per µg/dL cord PbB: Motor score: • Females: 0.48 (-1.55, 2.52), p=0.64 • Males: -0.70 (-2.90, 1.51), p=0.53
Rodrigues et al. 2016 Prospective study with cross-sectional analysis of PbB and fine motor score; n=524 children, 20–30 months	Median (P25, P75, maximum) • Sirajdikhan: 7.6 (5.5, 10.4) • Pabna: <LOD (<LOD, 3.8, 13.8)	BSID III	β score (SE) per child lnPbB (µg/L): Fine motor score: • Sirajdikhan: 0.07 (0.11), p=0.50 • Pabna: -0.07 (0.11), p=0.50
Silver et al. 2016 Prospective study; infants assessed for hearing at 2 days and vision at 6 weeks; maternal blood Pb collected at mid pregnancy and late pregnancy and in cord blood	Exposure for infants with hearing data: Gmean (SD) Mid-pregnancy: 2.4 (2.5) Late-pregnancy: 2.7 (2.3) Cord: <LOQ Exposure for infants with vision data: Gmean (SD) Mid-pregnancy: 2.4 (2.6) (n=1,038); Late-pregnancy: 2.9 (2.2) (n=1,058); Cord: <LOQ (n=949)	Hearing at age 2 days (ABR); vision at age 6 weeks (GVA)	Percent change in score relative to <2 µg/dL (late-pregnancy) reference group GVA score for PbB strata: • >3.8 µg/dL: -8.5 (-14.7, -2.4)* • 2 - 3.8 µg/dL: -7.2 (-13.3, -1.1)* ABR C-P ratio for PbB strata: • >3.8 µg/dL: 4.6 (1.8, 7.4)* • 2 - 3.8 µg/dL: 3.2 (0.0, 5.9)*

2. HEALTH EFFECTS

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Taylor et al. 2018 Prospective study; n=14,541 mother-infant pairs with follow-up of 1,558 children at age 7 years	Mean (SD) at gestation week 11 Mean (SD) 3.66 (1.55) Range: 0.20, 19.14	Motor skills (Movement Assessment Battery)	OR for scores per $\mu\text{g/dL}$ prenatal PbB: <ul style="list-style-type: none"> Heal to toe: 0.99 (0.74, 1.33), $p=0.93$ Beanbag: 0.88 (0.58, 1.32), $p=0.54$ Threading lace: 1.12 (0.83, 1.50), $p=0.47$ Peg board (preferred hand): 1.19 (0.88, 1.60), $p=0.26$ Peg board (non-preferred hand): 1.14 (0.85, 1.54), $p=0.37$
Tellez-Rojo et al. 2006 Prospective study; n=294 children (followed from birth to age 2 years)	Mean (SD): <ul style="list-style-type: none"> Cord: 4.85 (3.0) 12 months: 4.27 (2.14) 24 months: 4.28 (2.25) 	PDI	β per 1 in change in PbB: 12 months: <ul style="list-style-type: none"> <10 $\mu\text{g/dL}$: -0.01, $p=0.98$ ≥ 10 $\mu\text{g/dL}$: -1.19, $p=0.01^*$ 24 months: <ul style="list-style-type: none"> <10 $\mu\text{g/dL}$: -1.18, $p<0.01^*$ ≥ 10 $\mu\text{g/dL}$: 0.04, $p=0.89$
Zhou et al. 2017 Prospective study; n=139 mother-infant pairs followed from birth to 24–36 months	Gmean (95% CI) Mid-late pregnancy: 3.30 (3.05, 3.57)	Motor skills (Gesell Development Scale)	β (95% CI) for development quotient per $\mu\text{g/dL}$: All children: <ul style="list-style-type: none"> Gross motor: 3.31 (-6.11, 12.73) Fine motor: 0.49 (-11.27, 12.24)
Altered brain structure and chemistry			
Cecil et al. 2008 Prospective study; n=157 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	Mean (SD, range): <ul style="list-style-type: none"> 6 month–6.5 years: 13.3 (5.9, 4.6–37.2) 	Brain volume	Association ($p\leq 0.001$) between increasing childhood mean PbB and decreasing brain volume affecting 1.2% of the total gray matter. Effects were greater in males than females. Largest effects were in the anterior cingulate cortex.

2. HEALTH EFFECTS

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Cecil et al. 2011	Mean (SD, range):	Brain metabolism	Association ($p < 0.05$) between increasing childhood mean PbB and decreasing regional levels of gray matter N-acetyl aspartate, glutamate-glutamine, creatine and phosphocreatine, and white matter choline. Areas affected include the basal ganglia, cerebellum vermis, parietal white matter, and frontal white matter.*
Prospective study; n=159 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	<ul style="list-style-type: none"> 6 months–6.5 years: 13.3 (6.1, 4.7–37.2) 		

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 9 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.^cAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values < 0.05 unless otherwise noted in the table.

ABR = brainstem auditory response; ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; ASSQ = Autism Spectrum Screening Development Questionnaire; AUC = area under the curve; BRIEF = Behavior Rating Inventory of Executive Function; BSID = Bayley Scales of Infant Development CD = Conduct Disorder; CEM = Coarsened Exact Matching; CI = confidence interval; CKD = chronic kidney disease; CL = confidence limit; C-P = central-to-peripheral; CPT = Continuous Performance Test; ECDI = Early Child Development Inventory; EOG = End of Grade; EPDS = Edinburgh Postnatal Depression Scale; FSIQ = Full-Scale intelligence quotient; FTII = Fagan Test of Infant Intelligence; FWS = Filtered Word Subtest; GCI = General Cognitive Index; Gmean = geometric mean; GSD = geometric standard deviation; GVA = grating visual acuity; IQ = intelligence quotient; IQR = interquartile range; ISAT = Illinois Standard Achievement Test; K-ABC = Kaufman Assessment Battery for Children; LOD = limit of detection; LOQ = limit of quantitation; MDI = Mental Development Index; MFF = Matching Familiar Figures; MSEL = Mullen Scales of Early Learning; NA = not available; NBNA = Neonatal Behavioral Neurological Assessment; ND = not detected; ODD = Oppositional Defiant Disorder; OR = odds ratio; PALS-K = Phonological Awareness Literacy Screening-Kindergarten; Pb = lead; PDI = Psychomotor Development Index; PR = prevalence ratio; RR = relative risk; RT = reaction time; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; SE = standard error; SRDBS = Self-Reported Delinquent Behavior Survey; SRS = Social Responsiveness Scale; TRF = Teacher Report Form from the Child Behavior Checklist; TTS = Toddler Temperament Scales; UCL = upper confidence limit; VEP = visual evoked potential

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FSIQ was assessed at age 28–30 years in 43 members of the Boston prospective study cohort (Bellinger et al. 1992). The change in FSIQ was -1.89 points (95% CI: -3.00, -0.47) per $\mu\text{g/dL}$ increase in late child PbB (mean 6.7 ± 3.6 at age 4 years, 3.0 ± 2.7 at age 10 years). After adjustment for maternal IQ, the change in FSIQ was -1.11 (95% CI: -2.29, 0.06).

The largest study was a pooled analysis from seven individual prospective studies that evaluated FSIQ (Baghurst et al. 1992; Bellinger et al. 1992; Canfield et al. 2003; Dietrich et al. 1993a; Ernhart et al. 1989; Schnaas et al. 2000; Wasserman et al. 1997). The pooled cohort consisted for 1,333 children who were evaluated for FSIQ between ages 4.8 and 6 years (Lanphear et al. 2005, 2019). Co-variates considered in the analysis included study, maternal IQ, HOME score (Home Observation for Measurement of the Environment Inventory score), maternal education, marital status, birth weight, birth order, maternal age, race, and prenatal tobacco exposure. Of these, maternal IQ, HOME, and birth weight were included in the final models. When the full cohort was considered (PbB range 0.1–72 $\mu\text{g/dL}$), the adjusted change in FSIQ was loglinear, with greater changes in IQ per unit change in PbB at lower PbB levels. Several blood Pb metrics were explored in regression modeling, and slopes were significant for childhood, peak, lifetime average, or concurrent (with IQ testing) PbB. The model that used concurrent PbB had the highest r^2 (not reported). The covariate adjusted regression β for this model was -2.65 (95% CI: -3.69, -1.61) IQ points per 1 $\ln\text{PbB}$. The unadjusted β was -4.84 (-5.98, -3.69). The concurrent PbB model predicts a decrease of 6.2 points in FSIQ when PbB increased from 1 to 10 $\mu\text{g/dL}$. In a PbB stratum maximum $<7.5 \mu\text{g/dL}$, the mean change in FSIQ was -2.53 (95% CI -4.48, -0.58) per 1 $\mu\text{g/dL}$ change in PbB, and for a PbB stratum maximum $\geq 7.5 \mu\text{g/dL}$, the mean change in FSIQ was -0.15 (95% CI -0.23, -0.07) per 1 $\mu\text{g/dL}$. Re-analyses of the pooled cohort reported in Lanphear et al. (2005) have been conducted (Crump et al. 2013; EPA 2014e). EPA (2014e) made several corrections to the dataset and obtained β coefficients that were similar to those reported in Lanphear et al. (2005). The results of the EPA (2014e) reanalysis are presented in Table 2-30.

The model that used early childhood PbB (6–24 months) had the highest r^2 (0.6433), although the r^2 was similar to concurrent PbB (0.6414). A benchmark dose (BMD) analysis of the pooled data from Lanphear et al. (2005) estimated BMDLs (95% lower one-sided confidence limit on BMD) ranging from 0.1 to 1 $\mu\text{g/dL}$ for a 1% decrease in FSIQ for the best-fitting models (Budtz-Jorgensen et al. 2013). This BMD analysis provides supporting evidence that exposures to Pb may produce effects on cognitive function in populations whose PbBs are well below 5 $\mu\text{g/dL}$, and may extend to levels below 1 $\mu\text{g/dL}$.

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In addition to the seven prospective studies included in the Lanphear et al. (2005, 2019) pooled analysis, more recent prospective studies have evaluated associations between PbB and FSIQ in children (Braun et al. 2012; Chiodo et al. 2004; Jusko et al. 2008; Kordas et al. 2011; Min et al. 2009; Schnaas et al. 2006; Taylor et al. 2017; Table 2-30). Each of these studies found significant associations between increasing PbB and decreasing FSIQ in study populations that had mean PbBs <10 µg/dL. The largest of these studies combined four Mexico City birth cohorts for a total of 1,035 mother-infant pairs (Braun et al. 2012). Cognitive function assessed at age 4 years (McCarthy General Cognitive Index [GCI]) decreased with increasing PbB measured at age 2 years. The adjusted effect of concurrent PbB was estimated as -3.8 (95% CI: -6.3, -1.4) points when PbB increased by 10 µg/dL. Similar to the findings of the Lanphear et al. (2005, 2019) study, covariate adjustment decreased the regression β by approximately 40% (from -6.4 to -3.8). The cohort mean PbB was 4.6 µg/dL (5th–95th percentile range 1.3–13.4). Studies of smaller cohorts from Mexico City found similar associations (Kordas et al. 2011; Schnaas et al. 2006). Schnaas et al. (2006) estimated the effect size to be a -4.0 (95% CI: -6.37, -1.65) point change in FSIQ measured at ages 6–10 years in association with a natural log increase in maternal PbB; the cohort geometric mean was 7.3 µg/dL (95% CI: 1.5, 17.4). Kordas et al. (2011) estimated the effect size to be -0.6 (SE 0.2) for a 1 µg/dL increase in concurrent PbB (mean 8.1 µg/dL \pm 4.4 SE). Prospective studies conducted in Cleveland, Ohio (Min et al. 2009) and Rochester, New York (Jusko et al. 2008) also found similar effect sizes for the associations between increasing PbB and decreasing IQ. In the Rochester study, the changes in FSIQ were larger at lower PbB, consistent with the outcomes of the Lanphear et al. (2005) study (Jusko et al. 2008). For the PbB range 2.1–10 µg/dL, the change in FSIQ measured at age 6 years was -1.2 per 1 µg/dL increase in PbB. This decreased to -0.32 and -0.15 for the ranges 10–20 and 20–30 µg/dL, respectively. In the Cleveland study, the change was -0.50 \pm 0.20 (SE) in FSIQ measured at age 4 years per 1 µg/dL increase in concurrent PbB (Min et al. 2009). A study conducted in Detroit, Michigan estimated the change in FSIQ to be -0.20 per 1 SD change in PbB (Chiodo et al. 2004). The decrement was significant ($p \leq 0.05$) in PbB strata <7.5 and <10 µg/dL. Not all prospective studies have found evidence for decreasing FSIQ in association with increased PbB. One of the largest birth cohorts that has been studied is the Avon Longitudinal Study of Parents and Children (ALSPC), conducted in the United Kingdom (Taylor et al. 2017). This study followed a cohort of approximately 14,000 births. In a follow-up of 2,127 children at age 8 years, increasing maternal PbB (mean 3rd trimester PbB 3.67 \pm 1.46 SD) was associated with an increase in FSIQ in females and no change in FSIQ in males. The changes in FSIQ were 0.73 (95% CI: 0.13, 1.01) per 1 µg/dL increase in PbB in females and -0.29 (95% CI: -1.02, 0.44) in males. A prospective study of 609 mother-infant pairs, conducted in Canada, found that increasing cord PbB was associated with decreasing FSIQ when assessed in male children at age 3–4 years (Desrochers-Couture et al. 2018). The change in FSIQ in males was -2.61 points (95% CI: -4.66, -0.48) per 1 µg/dL

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and the change in females was -0.18 (-1.63, 1.21). The geometric mean cord PbB was 3.80 ± 1.86 (geometric standard deviation [GSD]).

Cross-sectional studies have also found associations between increasing PbB and FSIQ in children (Hong et al. 2015; Ruebner et al. 2019). A study conducted in South Korea evaluated PbB and FSIQ in 1,001 children 8–11 years of age (Hong et al. 2015). The estimated effect of PbB on FSIQ was -7.23 points (95% CI: -13.39, -1.07) per 10-fold increase in PbB. The 5th–95th percentile range for the cohort PbB was 0.53–6.16 µg/dL. A study of 412 children (median age 15 years) who were diagnosed with CKD found an association between increasing child PbB and decreasing FSIQ, after adjustment for CKD severity (Ruebner et al. 2019). The estimated effect of PbB on FSIQ was -2.1 (95% CI: -3.9, -0.2).

Cognitive function in early childhood—other than FSIQ. Several studies have examined outcomes other than IQ and have found associations between PbB and changes in cognitive function in children whose PbBs were <10 µg/dL (Table 2-30). These include prospective studies that used the same outcome metric, the BSID MDI, allowing comparison of outcomes across studies (Dietrich et al. 1986, 1987, 1989; Kim et al. 2013b; Polanska et al. 2018; Rodrigues et al. 2016; Tellez-Rojo et al. 2006). A prospective study of 884 children conducted in South Korea found inverse associations between PbB in late pregnancy (geometric mean 1.3 ± 1.5 , GSD) and MDI scores measured at age 6 months (Kim et al. 2013b). A prospective study of 294 children conducted in Mexico City found inverse associations between concurrent PbB (mean 4.27 ± 2.14 , SD) and MDI measured at 24 months in a PbB stratum <10 µg/dL (Tellez-Rojo et al. 2006). A prospective study conducted in Cincinnati, Ohio (approximately 190 infants) found declines in MDI scores at age 6 and 12 months in association with increasing maternal, neonatal, or infant PbB (Dietrich et al. 1986, 1987, 1989). A prospective study conducted in Poland (303 infants) found declines in MDI scores at age 2 years in males (but not females) in association with increasing cord PbB (range 0.24–5.65 µg/dL) (Polanska et al. 2018). A prospective study conducted in Bangladesh (324 infants) found declines in MDI scores at age 2–3 years in association with increasing child PbB (median 7.6 µg/dL, maximum 10.4 µg/dL) (Rodrigues et al. 2016).

Several large-scale retrospective studies linked academic performance for individual children with their corresponding blood Pb data recorded in state or local blood Pb registries (Blackowicz et al. 2016; Evens et al. 2015; Miranda et al. 2009; Shadbegian et al. 2019; Zhang et al. 2013; Table 2-30). Evens et al. (2015) linked individual 3rd grade Illinois Standard Achievement Test (ISAT) scores and PbB data (birth–72 months) for a population of 47,158 children in Chicago, Illinois. All children had PbB <10 µg/dL and the population mean was 4.8 ± 2.2 µg/dL (SD). Increasing PbB was inversely associated with decreasing

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covariate adjusted scores in math and reading. The adjusted relative risks (RRs) for failing scores was also significant for a 1 or 5 $\mu\text{g/dL}$ increase in PbB. A follow-up to this study of the same data from Chicago that focused on Hispanic children who had PbB $<10 \mu\text{g/dL}$ also found that increasing PbB was associated with decreasing scores in math and reading and significant RRs for failing scores (Blackowicz et al. 2016). Miranda et al. (2009) linked 4th grade reading End of Grade (EOG) scores and PbB data collected (birth–36 months) for a population of 57,678 children in North Carolina. The population mean PbB was 4.8 $\mu\text{g/dL}$ (range 1–16 $\mu\text{g/dL}$); 94% of children had PbB $<10 \mu\text{g/dL}$. Increasing PbB was associated with decreasing covariate adjusted scores in all PbB strata, the lowest of which was 2 $\mu\text{g/dL}$. The effect size (change in score/ $\mu\text{g/dL}$ PbB) increased with increasing PbB. Another study conducted in North Carolina analyzed data on PbB and standardized achievement scores of children in grades 3–8 (Shadbegian et al. 2019). Increasing PbB was associated with decreasing score percentiles in math and reading among children who had PbBs within the range $>1\text{--}5 \mu\text{g/dL}$, relative to children who had PbBs $<1 \mu\text{g/dL}$. Zhang et al. (2013) linked Michigan Educational Assessment Program (MEAP) scores and PbB data (birth–72 months) of age for a population of approximately 21,000 children in Detroit, Michigan. Covariate adjusted ORs for failing scores in mathematics, science, and reading were significant for PbB strata 1–5, 6–10, and $>10 \mu\text{g/dL}$. A cross-sectional study of data from NHANES III examined associations between PbB and scores on tests of cognitive function (Wide Range Achievement Test-Revised [WRAT-R], Wechsler Intelligence Scales for Children-Revised [WISC-R]) in approximately 5,000 children 6–16 years of age (Lanphear et al. 2000a). Increasing PbB was significantly associated with decreasing scores in reading in blood strata <5.0 , <7.5 , and $<10 \mu\text{g/dL}$. McLaine et al. (2013) examined associations between PbB (9–72 months) and kindergarten readiness assessed from Phonological Awareness Literacy Screening-Kindergarten (PALS-K) scores in approximately 3,400 children in Providence, Rhode Island. The population median PbB was 4.2 $\mu\text{g/dL}$ (interquartile range 2.9–6.0); 93% of children had PbB $<10 \mu\text{g/dL}$. Mean difference in covariate adjusted scores in blood strata 5–9 and $\geq 10 \mu\text{g/dL}$ compared to $<4 \mu\text{g/dL}$ were in the inverse direction and adjusted prevalence ratios for test failure was significant in both strata. Genetic variants of N-methyl-D-aspartate receptors (NMDAR subunits GRIN2A and GRIN2B) were effect modifiers on associations between increasing PbB (at age 8–12 years) and decreasing performance tests of learning, memory, and executive function at age 17 years (Rooney et al. 2018).

Altered mood and behavior. Numerous studies have examined possible associations between neonatal and child PbB risk of behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency (Table 2-30).

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Several studies have examined attention-deficit/hyperactivity disorder (ADHD) as an outcome, allowing comparisons of outcomes across studies (Arbuckle et al. 2016; Boucher et al. 2012; Braun et al. 2006; Choi et al. 2016; Desrochers-Couture et al. 2019; Froehlich et al. 2009; Geier et al. 2018; He et al. 2019; Hong et al. 2015; Huang et al. 2016; Ji et al. 2018; Joo et al. 2017; Park et al. 2016; Wang et al. 2008). Collectively, the ADHD studies indicate that risk of childhood ADHD increases in association with increasing PbB within the range of PbB <10 µg/dL (Table 2-30). Several case-control studies have found associations between increasing PbB and increasing OR for ADHD diagnosis in children (Joo et al. 2017; Park et al. 2016; Wang et al. 2008). In the largest case-control study (630 cases), conducted in China, covariate-adjusted ORs for ADHD in children 4–14 years of age were 4.92 (95% CI 3.47, 6.98) for the PbB range 5–10 µg/dL and 6.00 (4.11, 8.77) for PbB ≥10 µg/dL compared to <5 µg/dL (Wang et al. 2008). Associations between increasing PbB and increasing OR for ADHD diagnosis in children have also been found in several prospective studies (Boucher et al. 2012; Huang et al. 2016; Ji et al. 2008). In the largest prospective study (1,479 children, median age 9.6 years), conducted in Boston, ORs were estimated relative to PbB <2 µg/dL (Ji et al. 2018). The OR for the PbB range of 2–4 µg/dL was 1.08 (95% CI 0.81, 1.44), and the OR for the PbB range of 5–10 µg/dL was 1.73 (95% CI 1.09, 2.73). The OR (5–10 µg/dL relative to <5 µg/dL) for male children (OR 2.49, 95% CI 1.46, 4.26) was larger than for female children (OR 0.68, 95% CI 0.27, 1.69). A prospective study of 272 children (mean age 11 years) conducted in Nunavik, Canada found elevated covariate adjusted ORs of 4.01 (95% CI 1.06, 15.23) for a PbB stratum 1.6–2.7 µg/dL and 5.52 (95% CI 1.38, 22.12) for the stratum 2.7–12.8 µg/dL (Boucher et al. 2012). A longitudinal study examined ADHD outcomes of 2,159 South Korean children (ages 7–9 years) who did not exhibit ADHD symptoms at recruitment (Choi et al. 2016). Two years following baseline assessment, the covariate adjusted relative risk of ADHD was estimated to be 1.552 (95% CI 1.002, 2.403) for children having PbB >2.17 µg/dL compared to ≤2.17 µg/dL. The geometric mean PbB for the cohort was 1.62 µg/dL ±1.52 (GSD). Several cross-sectional studies have also found associations between concurrent PbB and risk of ADHD (Braun et al. 2006; Froehlich et al. 2009; Hong et al. 2014). A study of data on approximately 4,700 children (age 4–15 years) reported in the 1999–2002 NHANES found elevated risk of ADHD in association with concurrent PbB >2 µg/dL and a significant trend in risk with increasing PbB (Braun et al. 2006). Froehlich et al. (2009) examined data for children 8–15 years of age from the 2001–2004 NHANES. Covariate adjusted ORs of ADHD were elevated for the PbB stratum >1.3 µg/dL (compared to ≥0.8 µg/dL). A cross-sectional study conducted in South Korea examined associations between PbB and ADHD rating scores of 1,001 children of age 8–11 years (Hong et al. 2015). One log₁₀ increase of PbB was associated with increases in teacher-rated ADHD hyperactivity (OR 3.66; 95% CI 1.18, 6.13) and total ADHD score (OR 6.38; 95% CI 1.36, 11.40). The cohort geometric mean PbB was 1.8±1.4 µg/dL (SD).

Prospective studies have also provided evidence for associations between neonatal or early childhood PbB and other neurobehavioral outcomes, including neonatal behavior, emotional or temperament problems, anxiety or depression, sleep disorders, hyperactivity and impulsivity, autistic behavior, and delinquency (Dietrich et al. 2001; Fruh et al. 2019; Huang et al. 2016; Joo et al. 2018; Kim et al. 2016; Liu et al. 2014b, 2015b; Sioen et al. 2013; Stroustrup et al. 2016; Winter and Sampson 2017).

Altered neuromotor-neurosensory function. Numerous studies have examined possible associations between neonatal and child PbB and neuromotor or neurosensory function (Table 2-30). Several studies used the Psychomotor Development Index (PDI) score from the BSID, allowing comparison of results across studies (Dietrich et al. 1987, 1989; Kim et al. 2013b; Tellez-Rojo et al. 2006). Each study found inverse associations for PDI scores measured from 6 to 12 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Studies that repeatedly measured PDI scores longitudinally within the same birth cohorts found that associations observed at 6 months persisted to later ages (Dietrich et al. 1987, 1989, 1991; Tellez-Rojo et al. 2006). A prospective study conducted in China administered a neurobehavioral test battery to a birth cohort of 237 children at age 7 years (Chiodo et al. 2004). Significant declines in performance ($p \leq 0.05$) were observed in PbB strata that ranged from $<3 \mu\text{g/dL}$ at the lowest to $<10 \mu\text{g/dL}$; most tests that showed significant declines at $<10 \mu\text{g/dL}$, also showed declines at $<5 \mu\text{g/dL}$ ($p \leq 0.05$). A prospective study conducted in Nunavik, Canada evaluated fine motor control in a birth cohort at 5 years (Fraser et al. 2006). Significant changes in motor control assessed from sway and reaction times were associated with increasing concurrent PbB ($p \leq 0.01$). The cohort PbB mean was $5.3 \mu\text{g/dL} \pm 4.9$ (SD). This birth cohort also exhibited changes in visual evoked potentials that were associated in increasing cord PbB (Ethier et al. 2012). The cohort cord PbB mean was 4.6 ± 3.1 (SD). However, not all studies have found associations between PbB and neuromotor performance. A follow-up of a prospective birth cohort of approximately 14,500 pregnancies evaluated motor skills in 1,558 children at age 7 years (Taylor et al. 2018). Prenatal (gestation week 11) PbB was not associated with performance on a movement assessment battery (e.g., heel-to-toe, threading lace, peg board).

Several studies have examined associations between PbB and neurosensory function in infants or children (Ethier et al. 2012; Liu et al. 2018b; Silver et al. 2016). A prospective study conducted in Nunavik, Canada found changes in visual evoked potentials at age 5 years that were associated with increasing cord PbB (mean $4/6 \pm 3.1 \mu\text{g/dL}$) (Ethier et al. 2012). A prospective study of 315 mother-infant pairs conducted in China found associations between increasing prenatal PbB and brainstem auditory response measured at age 2 days and grating visual activity measured at age 6 weeks (Silver et al. 2016). Geometric mean

late-pregnancy PbB was 2.7 ± 2.3 (GSD) $\mu\text{g/dL}$. A cross-sectional study of 234 children (age 3–7 years), conducted in China, found that increasing PbB was associated with hearing loss (Liu et al. 2018b). The OR for hearing loss was 1.24 (95% CI 1.029, 1.486). The median PbB was 4.94 ± 0.20 (SE) $\mu\text{g/dL}$.

Altered brain structure and neurochemistry. A follow-up to the Cincinnati prospective study (Dietrich et al. 1986) estimated whole brain volumes and imaged brain metabolites in 157–159 adults at age 19–24 years (Brubaker et al. 2010; Cecil et al. 2008, 2011; Table 2-30). Decreasing covariate adjusted brain volume was associated with increased childhood mean PbB (measured between ages 6 months and 6 years). Brain volume reductions that were associated with childhood PbB compromised approximately 1.2% of the total gray matter and were more severe in males compared to females. The largest effects were observed in the anterior cingulate cortex. This region of the brain is involved in controlling executive function, mood, and decision-making. Increasing childhood PbB was also associated with decreasing concentrations of various metabolites in the brain known to be important in the supporting metabolic structural integrity of neurons (e.g., lipid metabolism and myelin production). These included decreased N-acetyl aspartate (NAA) in the basal ganglia and cerebellar hemisphere, decreased glutamate-glutamine in the vermis and parietal white matter, decreased creatine and phosphocreatine in the basal ganglia, and decreased cholines in the cerebellum, parietal white matter, and frontal white matter. These changes in association with childhood PbB suggest that childhood Pb exposure may be indicators of longer-term changes in brain glutamate-associated lipid metabolism or neuronal architecture (Cecil et al. 2011).

Associations Between Bone Pb and Neurological Effects in Children. Few studies have been conducted to assess possible associations between bone Pb and neurological function in children (Table 2-31). Prospective studies of outcomes in children of mother-infant pairs have found associations between maternal or child bone Pb cognitive function (Campbell et al. 2000b; Gomaa et al. 2002; Needleman et al. 1996; Wasserman et al. 2003; Xu et al. 2015). Increasing bone Pb measured at age 24 months was associated with decrements in cognitive development (Gomaa et al. 2002) and behaviors indicative of attention deficit hyperactivity disorder assessed at age 7–15 years (Xu et al. 2015). Increasing child bone Pb measured later in childhood (ages 11–14 years) was associated with decrements in language processing (Campbell et al. 2000b); full scale, verbal, and performance IQ (Wasserman et al. 2003); and delinquent, aggressive, internalizing, externalizing behaviors (Needleman et al. 1996). A case-control study of adjudicated delinquency at age 12–18 years found associations between increasing bone Pb and delinquency (Needleman et al. 2002). A prospective study found associations between increasing bone Pb and difficult temperament at age 24 months (Stroustrup et al. 2016).

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Table 2-31. Associations Between Bone Pb and Neurological Outcomes in Children

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Campbell et al. 2000b	156 males, age: 11–14 years	↑ T	–	–	Language processing
Gomaa et al. 2002	197 mother-infant pairs	↑ P ^a 0 T ^a	–	–	24-month MDI ^b
Needleman et al. 1996	301 males, age: 9–13 years	–	–	↑ T	Delinquent, aggressive, internalizing, externalizing behaviors
Needleman et al. 2002	194 male cases, 145 controls, age: 12–18 years	–	–	↑ T	Adjudicated delinquency
Stroustrup et al. 2016	948 mother-infant pairs, 760 children, age: 24 months	–	–	↑ T	Difficult temperament
Wasserman et al. 2003	167 children, age: 10–12 years	↑ T	–	–	IQ (full scale, verbal, performance) ^c
Xu et al. 2015	197 mother-infant pairs	–	–	↑ P ^a	Attenuation of effect of maternal self-esteem on ADHD assessed at age 7–15 years ^d

^aMaternal bone lead measured within 1 month of birth.^bBayley Scale.^cWechsler Intelligence Scale for Children-III.^dMaternal self-esteem was evaluated with Coopersmith Self-Esteem Inventory. ADHD was evaluated with Conners' Parent Rating Scale-Revised and Behavior Rating Inventory of Executive Function.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; ADHD = Attention deficit hyperactivity disorder; C = calcaneus bone; MDI = Mental Developmental Index; P = patella; Pb = lead; T = tibia; O = other

Effects at Blood Pb Levels ≤10 µg/dL in Adults. Numerous longitudinal and large cross-sectional studies in adults provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in association with exposures that result in PbB <10 µg/dL,

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with some studies showing effects in the 3–5 µg/dL range. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead*, Table 10. Cognitive, neuromotor, and neurosensory outcomes have been evaluated with tests of memory, learning, executive function, reaction time, walking speed, and tremor. Pb exposure has been associated with risk of various psychiatric symptoms including anxiety, depression, and schizophrenia, and with risk of ALS. In some studies, associations were found between outcomes and PbB and/or bone Pb. Several studies have examined cohorts of people who had mean ages within the range 50–70 years. Studies of cognitive function in elderly populations must control for factors that contribute to age-related decrements in function, including confounding from the relationship between age and bone Pb, which increases with age. Longitudinal studies offer advantages over cross-sectional studies in that they can provide measurement changes in function of individual subjects with age.

Cognitive function. Numerous studies have examined possible associations between Pb exposure and cognitive function in adults (Table 2-32). Most of these studies have found associations between increasing Pb exposure, indicated by blood or bone Pb, and indications of decreased cognitive function (Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Przybyla et al. 2017; Seegal et al. 2013; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006, 2009; Wright et al. 2003b). However, not all studies have found associations (Kreig et al. 2005; Yu et al. 2019b). One of the largest cross-sectional studies analyzed data from NHANES III (1988–1994) found no associations between PbB and performance on neurobehavioral tests (Krieg et al. 2005). This study compared scores from several tests from the Neurobehavioral Evaluation System (NBES) and concurrent PbB in approximately 5,700 adults (age 20–50 years). Implemented tests measured processing speed, attention, learning, and memory (reaction time, symbol-digit substitution, serial digit learning). The geometric mean PbB was 2.51 µg/dL (range 0.7–42) and 96% of the cohort was <10 µg/dL. No significant associations (defined as $p \leq 0.05$) between PbB and cognitive outcomes were found. However, associations between PbB and cognitive performance may be stronger in elderly adults. An examination of a smaller cohort from the NHANES 1999–2000, restricted to ages ≥ 60 years ($n=498$), found an association between increasing PbB and decreasing scores on short-term memory (digit symbol test) (Przybyla et al. 2017). The geometric mean PbB in this study was 2.17 µg/dL. Several studies have examined smaller cohorts from longitudinal studies designed to evaluate health in aging populations. Studies of male cohorts from the Normative Aging Study have found significant ($p \leq 0.05$) associations between increasing blood and/or bone Pb and

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Cognitive abilities			
Krieg et al. 2005	Gmean (range): 2.51 (0.7, 41.8)	Simple visual reaction time	No associations between PbB and performance scores
Cross-sectional study; n=5,662 adults, age 20–59 years			<ul style="list-style-type: none"> • Mean reaction time: p=0.24
		Symbol-digit substitution	<ul style="list-style-type: none"> • Mean total latency: p=0.27 • Number of errors: p=0.82
		Serial digit learning	<ul style="list-style-type: none"> • Trials to criterion: p=0.26 • Total score: p=0.24
Muldoon et al. 1996	Mean (SD):	Trailmaking B	<ul style="list-style-type: none"> • Urban <ul style="list-style-type: none"> ◦ Medium PbB OR: 0.97 (0.40, 2.40) ◦ High PbB OR: 0.79 (0.20, 3.04) • Rural <ul style="list-style-type: none"> ◦ Medium PbB OR: 2.05 (1.05, 4.02)* ◦ High PbB OR: 2.60 (1.04, 6.49)*
Cross-sectional study; n=530 adult women, mean age 70 years	<ul style="list-style-type: none"> • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7 	Digit symbol (correct)	<ul style="list-style-type: none"> • Urban <ul style="list-style-type: none"> ◦ Medium PbB OR: 0.61 (0.25, 1.50) ◦ High PbB OR: 0.64 (0.16, 2.47) • Rural <ul style="list-style-type: none"> ◦ Medium PbB OR: 2.03 (1.06, 3.88)* ◦ High PbB OR: 3.73 (1.57, 8.84)*
		Incidental memory	<ul style="list-style-type: none"> • Urban <ul style="list-style-type: none"> ◦ Medium PbB OR: 0.50 (0.22, 1.16) ◦ High PbB OR: 0.99 (0.28, 1.16) • Rural <ul style="list-style-type: none"> ◦ Medium PbB OR: 1.37 (0.77, 2.41) ◦ High PbB OR: 1.89 (0.83, 3.41)

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^c
Payton et al. 1998	Mean (SD):	Pattern recognition	• β : 0.074 (0.032), $p=0.02^*$
Longitudinal study; n=141 males, mean age 67 years	• 5.5 (3.5)	Vocabulary	• β : -0.841 (0.20), $p=0.0001^*$
	• Q1: 1.4	Word list memory	• β : -0.182 (0.086), $p=0.036^*$
	• Q2: 3.5	Boston naming test	• β : -0.036 (0.016), $p=0.028^*$
	• Q3: 5.4	Verbal fluency	• β : -0.230 (0.120), $p=0.09$
	• Q4: 9.8		
Power et al. 2014	Mean (SD):	Overall cognition	β for 1-age year change in score per 1 SD PbB: -0.013 (-0.044, 0.017)
Longitudinal study; n=584 adults females, mean age 61 years	• 2.9 (1.9)	Verbal memory	β for 1-age year change in score per 1 SD PbB: 0.006 (-0.037, 0.050)
	Tibia Pb ($\mu\text{g}/\text{g}$): Mean (SD):		
	• 10.5 (9.7)		
	Patella Pb ($\mu\text{g}/\text{g}$) mean (SD):		
	• 12.6 (11.7)		
Przybyla et al. 2017	Gmean (range): 2.17 (0.4, 16.4)	Digit symbol (correct)	β per lnPbB $\mu\text{g}/\text{dL}$: -0.10 (-0.20, -0.006), $p=0.04$
Cross-sectional study; n=498 adults, age 60–84 years			
Seo et al. 2014	Gmean (range):	Verbal memory	Accuracy % (SD), exposed versus control:
Cross-sectional study; n=31 retired female Pb workers, mean age 60.4 years, and 34 controls	Exposed: 4.07 (0.88–13.5) Controls: 2.00 (1.24–6.47)		• 1-back test: 55.9 (19.8) versus 65.4 (19.4), $p=0.056$
			• 2-back test: 61.4 (20.1) versus 77.2 (15.6), $p=0.001^*$

2. HEALTH EFFECTS

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^c
Shih et al. 2006		Language	<ul style="list-style-type: none"> • B per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0083 (0.0023), $p \leq 0.01^*$
Cross-sectional study; n=985 adults, mean age 59.4 years	Mean (SD): <ul style="list-style-type: none"> • 3.46 (2.23) Tibia Pb ($\mu\text{g}/\text{g}$) mean (SD): <ul style="list-style-type: none"> • 18.72 (11.24) 	Processing speed	<ul style="list-style-type: none"> • β per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0042 (0.0021), $p < 0.01^*$
		Eye-hand	<ul style="list-style-type: none"> • β per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0079 (0.0020), $p \leq 0.01^*$
		Executive function	<ul style="list-style-type: none"> • β per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0075 (0.0019), $p \leq 0.01^*$
		Verbal memory and learning	<ul style="list-style-type: none"> • β per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0078 (0.0024), $p \leq 0.01^*$
		Visual memory	<ul style="list-style-type: none"> • β per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0067 (0.0023), $p \leq 0.01^*$
		Visuoconstruction	<ul style="list-style-type: none"> • β per 1 $\mu\text{g}/\text{g}$ tibia Pb: -0.0122 (0.0027), $p \leq 0.01^*$
Weisskopf et al. 2007		Vocabulary	<ul style="list-style-type: none"> • β per 3 $\mu\text{g}/\text{dL}$ increase in PbB: -1.26 (-2.08, -0.44), $p = 0.003^*$
Longitudinal study cohort, n=1,089 males, mean age 68.7 years	Median (IQ range): <ul style="list-style-type: none"> • 5 (3–6) Tibia Pb ($\mu\text{g}/\text{g}$) median (IQ range): <ul style="list-style-type: none"> • 20 (13–28) Patella Pb ($\mu\text{g}/\text{g}$) median (IQ range): <ul style="list-style-type: none"> • 25 (17–37) 	Visuoconstruction (patella Pb)	<ul style="list-style-type: none"> • β per IQR: -0.067 (-0.11, -0.02), $p = 0.0041^*$
		Pattern comparison latency (tibia Pb)	<ul style="list-style-type: none"> • β: 0.079 (0.04, 0.12), $p = 0.0004^*$
Weuve et al. 2006		Cognitive function	Change in MMSE score per IQR in PbB, 3 $\mu\text{g}/\text{dL}$: <ul style="list-style-type: none"> • ALAD-2: IQR: -0.29 (-0.56, -0.02)* • ALAD wildtype: IQR: -0.05 (-0.16, 0.06)
Longitudinal study cohort, n=915 males, mean age 68.7 years	Median (IQ range): <ul style="list-style-type: none"> • 5.2 (2.9) • 94% <10 		
Weuve et al. 2009		Cognitive function	Change in score per 1 SD in PbB or bone Pb: <ul style="list-style-type: none"> • PbB: -0.016 (-0.071, 0.039), $p = 0.57$ • Tibia: -0.051 (-0.099, -0.003), $p = 0.04^*$ • Patella Pb: -0.033 (-0.080, 0.014), $p = 0.17$
Longitudinal study cohort, n=587 females, mean age 61 years	Mean (SD): <ul style="list-style-type: none"> • 2.9 (1.9) Tibia Pb ($\mu\text{g}/\text{g}$) median (SD): <ul style="list-style-type: none"> • 10.5 (9.7) 		

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Patella Pb (µg/g) median (SD): <ul style="list-style-type: none"> 12.6 (11.6) 			
Wright et al. 2003b	Mean (SD):	MMSE score	Adjusted OR with 1 µg/dL increase in PbB or 1 µg/g increase in bone Pb:
Longitudinal study cohort, n=736 males, mean age 68.2 years	• All: 4.5 (2.5)		• PbB: 1.21 (1.07, 1.36)*
	• Q1: 2.5		• Patella Pb: 1.02 (1.00, 1.03)*
	• Q2: 4.0		• Tibia Pb: 1.02 (1.00, 1.04)*
	• Q3: 5.9		
	• Q4: 8.9		
	Tibia Pb (µg/g) median (SD):		Effect of age increased with increasing PbB. β for age with increasing Pb for PbB quartile:
	• 22.4 (15.3)		• Q1 -0.04 (-0.07, -0.02)*
	Patella Pb (µg/g) median (SD):		• Q2 -0.04 (-0.08, -0.01)*
	• 29.5 (21.2)		• Q3 -0.09 (-0.13, -0.06)*
			• Q4 -0.12 (-0.17, -0.02)*
Yu et al. 2019b	Gmean (IQR): 2.47 (2.00, 3.00)	Digit symbol (mean total latency)	β per log ₁₀ PbB: 5.4% (-0.4, 11.5), p=0.066
Cross-sectional study; n=339 males, mean age 28.6 years		Stroop reaction time incongruent trials	β per log ₁₀ PbB: 5.1% (-4.5, 15.6), p=0.30
		Stroop reaction time congruent trials	β per log ₁₀ PbB: -1.2% (-10.4, 9.0), p=0.81
		Stroop interference effect	β per log ₁₀ PbB: 23.0% (-15.4, 78.9), p=0.28

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Mood and behavior			
Bouchard et al. 2009	Gmean±GSD (range):	Major depressive disorder	• Adjusted ORs for PbB for Q5 relative to Q1: 2.32 (1.13, 4.75); p-trend=0.05*
Cross-sectional study; n=1,987 adults (age 20–39 years)	• 1.24 (1.96)		
	• 99%≤10		• Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 2.93 (1.24, 6.92); p-trend=0.03*
	• Q1: 0.6		
	• Q2: 0.9		
	• Q3: 1.2	Panic disorder	• Adjusted ORs for PbB for Q5 relative to Q1: 4.94 (1.32, 18.48); p-trend=0.02*
	• Q4: 1.3		• Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 9.57 (1.28, 71.43); p-trend=0.01*
	• Q5: 3.0		
Generalized anxiety disorder			
		• Adjusted ORs for PbB for Q5 relative to Q1: 1.53 (0.39, 5.96); p-trend=0.78	
		• Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 1.59 (0.19, 13.31); p-trend=0.44	
Buser and Scinicariello 2017	Cohort stratified into PbB quartiles:	Depression	Adjusted OR for depression symptoms in adult females (age 20–47 years) associated with increasing PbB:
Cross-sectional study of 3,905 adults (age ≥20 years) from NHANES 2011–2012	• Q1: <0.7		• Q3: 1.86 (1.01, 3.41, p<0.05*
	• Q2: 0.70–1.06		• Q4: 2.97 (1.01, 8.74), p<0.05*
	• Q3: 1.07–1.67		
	• Q4: >1.67		
Fan et al. 2020	Mean (SD): 3.229 (2.357)	Depression symptoms (score on 30-point Geriatric Depression Scale ≥11)	OR for depression for PbB quartiles relative to Q1:
Cross-sectional study; n=994 adults, age >60 years	• Q1: <2.027		• Q2: 1.28 (0.79, 2.08), p=0.315
	• Q2: 2.027, 2.677		• Q3: 1.36 (0.84, 2.22), p=0.216
	• Q3: 2.677, 3.058		• Q4: 2.03 (1.23, 3.35), p=0.006*
	Q4: ≥3.058		• p-trend=0.007*

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Golub et al. 2010	Cohort stratified into PbB quartiles:		Adjusted OR for depression symptoms was elevated in PbB quartile 3 (95% CI):
Cross-sectional study; 4,195 adults (age ≥20 years) from NHANES 2005–2006	<ul style="list-style-type: none"> • Q1: ≤0.88 • Q2: 0.89–1.40 • Q3: 1.41–2.17 • Q4: 2.18–26.4 		<ul style="list-style-type: none"> • Q3: 1.25 (1.07, 1.47)*
Li et al. 2017a	Gmean (range): 3.99 (0.80, 14.84)	Depression symptoms	β per log ₁₀ PbB:
Cross-sectional study; n=1,931 pregnancies (age 13–42 years)			<ul style="list-style-type: none"> • Full cohort: 0.03 (-0.05, 0.10), p=0.466 • PbB ≤2.57: 0.34 (0.12, 0.56), p=0.002* • PbB >2.57: -0.09 (-0.19, 0.02), p=0.113
		Anxiety symptoms	β per log ₁₀ PbB:
			<ul style="list-style-type: none"> • Full cohort: 0.01 (-0.06, 0.08), p=0.770 • PbB ≤2.57: 0.25 (0.04, 0.46), p=0.019* • PbB >2.57: -0.08 (-0.18, 0.02), p=0.136
		Depression or anxiety symptoms (Global Severity Index)	β per log ₁₀ PbB:
			<ul style="list-style-type: none"> • Full cohort: 0.01 (-0.05, 0.07), p=0.815 • PbB ≤2.57: 0.22 (0.05, 0.40), p=0.013* • PbB >2.57: -0.07 (-0.16, 0.01), p=0.100
Opler et al. 2004	Cohort stratified into <15 or ≥15 µg/dL based on 2 nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: 2.43 (0.99, 5.96), p=0.051
Case-control study; n=44 schizophrenia cases and 75 matched controls from birth cohorts			
Opler et al. 2008	Cohort stratified into <15 or ≥15 µg/dL based on 2 nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: 1.92 (1.05, 3.87), p=0.03*
Case-control study; n=71 schizophrenia cases and 129 matched controls			

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Rajan et al. 2007 Longitudinal study cohort, n=1,075 males, mean age 67.1 years	Mean (SD): • All: 6.2 (4.1) Tibia Pb (µg/g) median (SD): • 22.1 (13.8) Patella Pb (µg/g) median (SD): • 31.4 (19.6)	Somatization, tibia Pb	Adjusted OR for inter quartile increases in tibia Pb (14 µg/g) or patella Pb (20 µg/g): 1.21 (1.01, 1.46)*
		Global severity index, patella Pb	OR: 1.23 (1.02, 1.47)*
Rhodes et al. 2003 Longitudinal study cohort, n=526 males, mean age 67.1 years	Mean (SD): • 6.3 (4.2) Tibia Pb (µg/g) median (SD): • 21.9 (13.5) Patella Pb (µg/g) median (SD): • 32.1 (19.8)	Phobic anxiety	Adjusted OR for inter quintile increases in patella Pb (8.9 µg/dL: 1.91 (1.01, 3.61)*
		Combined symptoms	Adjusted OR for inter quintile increases: • PbB OR: 2.91 (1.39, 6.09)* • Tibia Pb OR: 2.08 (1.06, 4.07)* • Patella Pb OR: 3.62 (1.62, 8.08)*
Scinicariello and Buser 2015 Cross-sectional study of 2,892 adults (age 20–39 years) from NHANES 2007–2010	PbB: Gmean (GSD) • 0.96 (0.02).	Depression	Adjusted OR for depression symptoms was not associated with increasing PbB (ORs were not reported).

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Neuromotor neurosensory function			
Casjens et al. 2018	Median (% >9)	Olfaction (score on 12-point odor identification test ≤7)	Proportional OR for PbB stratum relative <5.0 µg/dL:
Longitudinal study; n=1,188 males, age 55–86 years at follow-up	<ul style="list-style-type: none"> Baseline: 3.29 (2.27%) 11-year follow-up: 2.59 (0.84%) 		Baseline:
			<ul style="list-style-type: none"> 5–<9 µg/dL: 0.91 (0.65, 1.28) ≥9 µg/dL: 1.96 (0.94, 4.11)
		Follow-up:	
		<ul style="list-style-type: none"> 5.0–<9.0 µg/dL: 1.04 (0.55, 1.94) ≥9.0 µg/dL: 1.57 (0.47, 5.19) 	
Dexterity (finger tapping errors)			
		OR (95% CI) for impaired performance <5.0 µg/dL:	
		<ul style="list-style-type: none"> 5.0 to <9.0 µg/dL: 0.87 (0.53, 1.44) ≥9.0 µg/dL: 1.35 (0.49, 3.70) 	
		Follow-up:	
		<ul style="list-style-type: none"> 5.0–<9.0 µg/dL: 2.63 (1.26, 5.94)* ≥9.0 µg/dL: 0.80 (0.14, 4.59) 	
Hwang et al. 2009	Mean (SD): 5.43 (3.46)	Hearing loss	Adjusted OR for hearing loss (>25 dB) at 3,000–8,000 Hz in PbB categories relative to ≤4 µg/dL:
Cross-sectional study; n=259 male steel workers, mean age 36.0 years			Loss at 3,000 Hz
			<ul style="list-style-type: none"> 4–7 µg/dL: 0.75 (0.17, 3.29) ≥7 µg/dL: 4.49 (1.28, 15.8); p<0.005*
		Loss at 4,000 Hz:	
		<ul style="list-style-type: none"> 4–7 µg/dL: 3.54 (1.40, 8.97)* (p-value not reported) ≥7 µg/dL: 6.26 (2.35, 16.6); p<0.005* 	
		Loss at 6,000 Hz:	
		<ul style="list-style-type: none"> 4–7 µg/dL: 2.11 (0.94, 4.47) ≥7 µg/dL: 3.06 (1.27, 7.39); p<0.05* 	

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^c
Huh et al. 2018 Cross-sectional study; n=2,387 adults, age 19–85 years	Gmean (95% CI): 2.46 (2.41, 2.52)	Hearing loss (pure tone threshold >25 dB)	OR per doubling of PbB (95% CI): <ul style="list-style-type: none"> Low frequency: 0.91 (0.52, 1.61) Speech frequency: 1.21 (0.72, 2.04) High frequency: 1.88 (1.11, 3.17)*
Ji et al. 2013 Cross-sectional study; n=1,795 males and 1,798 females, age >50 years (median 61.2)	Mean (SD): <ul style="list-style-type: none"> Females: 2.17 (0.06) Males: 3.18 (0.12) 	Walking speed	Mean change in walking speed (ft/sec) for PbB quintile relative to Q1 (≤ 1.2 $\mu\text{g}/\text{dL}$): <ul style="list-style-type: none"> PbB 1.3–≤ 1.6, β: -0.024 (-0.112, 0.064), p=0.58 PbB 1.7–≤ 2.1, β: -0.027 (-0.118, 0.063), p=0.54 PbB 2.2–≤ 2.9, β: -0.104 (-0.187, -0.021), p=0.02* PbB 3.3–≤ 53.0, β: -0.114 (-0.191, -0.038), p=0.01* p-trend=0.005*
Ji et al. 2015 Longitudinal study cohort, n=807 males, mean age 69 years	Mean (SD): 5.0 (2.7) <ul style="list-style-type: none"> % <10: 96% Bone Pb, $\mu\text{g}/\text{g}$ (SD) <ul style="list-style-type: none"> Patella: 28.0 (18.4) Tibia: 21.2 (13.3) 	Tremor	OR for tremor by PbB quintile: <ul style="list-style-type: none"> Q5 (8–28), PbB: 0.84 (0.38, 1.86), p=0.72 Q5 (40–165), patella Pb: 0.83 (0.31, 2.19), p=0.41 Q5 (30–126), tibia Pb: 1.08 (0.46, 2.53), p=0.60

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$)	Outcome evaluated	Result ^c
Kang et al. 2018			
Cross-sectional study; n=6,409 adults, age 20–87 years	Cohort stratified into PbB quartiles Females, weighted mean (SE)	Hearing loss (females)	<ul style="list-style-type: none"> • Q2: 0.947 (0.606, 1.477) • Q3: 1.013 (0.698, 1.471) • Q4: 1.502 (1.027, 2.196)*
	<ul style="list-style-type: none"> • Q1: 1.12 (0.01) • Q2: 1.61 (0.01) • Q3: 2.11 (0.01) • Q4: 3.03 (0.03) Males, weighted mean (SE) <ul style="list-style-type: none"> • Q1: 1.56 (0.01) • Q2: 2.22 (0.01) • Q3: 2.82 (0.01) • Q4: 4.22 (0.08) 	Hearing loss (males)	<ul style="list-style-type: none"> • Q2: 1.368 (1.006, 1.859)* • Q3: 1.402 (1.005, 1.955)* • Q4: 1.629 (1.161, 2.287)*
Muldoon et al. 1996			
Cross-sectional study; n=530 adult women, mean age 70 years	Mean (SD): <ul style="list-style-type: none"> • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7 	Pegboard	OR for poor performance (low PbB reference) in the rural cohort: ANOVA, p=0.98 <ul style="list-style-type: none"> • Medium PbB OR: 1.37 (0.71, 2.65) • High PbB OR: 1.16 (0.45, 3.01)
		Upper extremity	ANOVA, p<0.01, in the rural cohort <ul style="list-style-type: none"> • Medium PbB: OR: 1.39 (0.73, 2.65) • High PbB: OR: 2.43 (1.01, 5.83)*
		Lower extremity	ANOVA, p<0.01, in the rural cohort <ul style="list-style-type: none"> • Medium PbB OR: 1.29 (0.68, 2.47) • High PbB OR: 2.84 (1.19, 6.74)*

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Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Neurological disease			
Fang et al. 2010	Mean (range):	ALS	Adjusted OR for ALS for doubling of PbB:
Case-control study; n=184 male ALS cases and 194 matched controls, mean age 63 years	<ul style="list-style-type: none"> Controls: 1.76 (0.32–6.90) Cases: 2.41 (0.72–7.58) 		<ul style="list-style-type: none"> All cases (n=184): 1.9 (1.3, 2.7)* Excluding progressive muscular atrophy and primary lateral sclerosis (n=151): 1.8 (1.2, 2.5)*
Kamel et al. 2002	Mean (range):	ALS	Adjusted OR for ALS (for a 1-µg/dL increase in PbB: 1.9 (1.4, 2.6)*
Case-control study; n=109 ALS cases and 256 matched controls, age 30–80 years	<ul style="list-style-type: none"> Cases: 3 of 194 had PbB >10 Controls: <10 µg/dL 		<ul style="list-style-type: none"> Adjusted OR for ALS relative to <2 µg/dL: <ul style="list-style-type: none"> 3–4 µg/dL: 14.3 (3.0, 69.3)* 5–14 µg/dL: 24.5 (4.3, 139.3)*

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 10 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.^cAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

ALA = aminolevulinic acid; ALAD-2 = delta-aminolevulinic acid dehydratase allele; ALS = amyotrophic lateral sclerosis; ANOVA = analysis of variance; CI = confidence interval; CL = confidence limit; Gmean = geometric mean; GSD = geometric standard deviation; IQ = intelligence quotient; IQR = interquartile range; MMSE = Mini-Mental Status Examination; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

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decreasing scores on cognitive tests, including short-term memory, verbal memory, and visuoconstruction (Payton et al. 1998; Weisskopf et al. 2007; Weuve et al. 2006). Cohort sizes in these studies ranged from approximately 600 to 1,100 and the mean PbB ranged from 2.9 ± 1.9 to 5.5 ± 3.5 $\mu\text{g/dL}$. Weuve et al. (2006) found that decreases in cognitive performance were associated with PbB in a cohort of ALAD-2 carriers, but not in a cohort that carried the wildtype ALAD allele. Studies of female cohorts (approximately 600 subjects) from the longitudinal Nurses' Health Study have found mixed outcomes (Power et al. 2014; Weuve et al. 2009). Weuve et al. (2009) found significant association between increasing tibia Pb, but not PbB, and scores on a telephone survey of cognitive function (the Telephone Interview for Cognitive Status, TIC). The TIC has been used to assess memory and executive function and has been used to evaluate dementia. The effect size was -0.051 (95% CI -0.099 , -0.003) points per 1 SD of tibia Pb. Power et al. (2014) used the same telephone survey instrument and found no associations between blood or bone Pb and cognitive function; the effect size for PbB was -0.013 (95% CI: -0.044 , 0.017) and the cohort mean PbB was 2.9 ± 1.9 (SD) $\mu\text{g/dL}$. A cross-sectional study of approximately 1,000 adults from the Boston Memory Study found inverse associations ($p \leq 0.05$) between performance on cognitive tests and increasing tibia Pb, but not for PbB (Shih et al. 2006). The cohort mean blood Pb was 3.46 ± 2.2 (SD) $\mu\text{g/dL}$. Cognitive function evaluated included language, processing speed, executive function, verbal memory and learning, and visuoconstruction. The effect sizes were substantially attenuated by race/ethnicity and years of educational and were no longer significant ($p < 0.05$) when adjusted for these covariates. A cross-sectional study of approximately 500 adult females from the Study of Osteoporotic Fractures found significant associations ($p \leq 0.05$) between performance on cognitive tests and increasing PbB (Muldoon et al. 1996). The odds of performing worse on visual attention and short-term memory tests were significantly decreased ($p \leq 0.05$) in a PbB stratum 4–7 and to >7 $\mu\text{g/dL}$ compared to stratum <4 $\mu\text{g/dL}$. A cross-sectional study of 339 newly hired male Pb workers did not find significant associations between PbB ($p \geq 0.05$) and performance on tests that measured attention, memory, and processing speed (Stroop test, Symbol Digit Test) (Yu et al. 2019b). The geometric mean PbB was 2.47 $\mu\text{g/dL}$.

Altered mood and behavior. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and symptoms of psychiatric disorders (Table 2-32). Several studies have analyzed cross-sectional data from NHANES to explore associations between depression symptoms and PbB (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Scinicariello and Buser 2015). Three studies found associations between PbB and depression in adult populations that had geometric mean PbBs that were $2\text{--}3$ $\mu\text{g/dL}$ compared to populations that have PbBs <1 (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010). Buser and Scinicariello (2017) found stronger

associations in adult women than in men. Cross-sectional studies in other populations have found significant associations between PbB and symptoms of depression or anxiety (Fan et al. 2020; Li et al. 2017a). The Fan et al. (2020) study was restricted to adults >60 years (n=994) and found that increasing PbB was associated with increasing scores on the Geriatric Depression Scale. The OR for categorization as depressed was 2.04 (95% CI: 1.23, 3.35) in the upper quartile PbB stratum (≥ 3.06 $\mu\text{g/dL}$). The Li et al. (2017a) study examined a cross-sectional cohort of 1,931 pregnancies (age range 13–42 years) for depression, anxiety, and psychological stress. Increasing PbB was associated with increasing scores on depression and anxiety assessments; however, the association was stronger in the PbB stratum ≤ 2.57 $\mu\text{g/dL}$ compared to a higher stratum > 2.57 $\mu\text{g/dL}$. Associations between psychiatric disorders and Pb exposure metrics have also been studied in longitudinal studies (Rajan et al. 2007; Rhodes et al. 2003). Two studies of cohorts from the Normative Aging Study found significant ORs for blood or bone Pb and various psychiatric symptoms in males (mean age 67 ± 7 , SD), including somatization, phobic anxiety, and composite indices of distress. Mean PbBs in these cohorts were 6 ± 4 (SD) $\mu\text{g/dL}$. Associations between PbB and psychiatric disorders have also been found in case-control studies (Opler et al. 2004, 2008). The largest was a study of 71 schizophrenia cases and 129 matched controls (Opler et al. 2008). The adjusted OR for schizophrenia was 1.92 (95% CI 1.05, 3.87) for the PbB stratum ≥ 15 $\mu\text{g/dL}$ compared to < 15 $\mu\text{g/dL}$. Because individual PbB data were not available, subjects were categorized into the high (< 15 $\mu\text{g/dL}$) or low (≥ 15 $\mu\text{g/dL}$) PbB categories based on measurements of serum ALA and a regression model relating PbB and ALA derived from a different population (Graziano et al. 1990). Although the accuracy of the method for assigning subjects from Graziano et al. (1990) into low or high categories was, on average, approximately 90%, uncertainty in the actual regression model is likely to have resulted in some misclassification of individuals.

Altered neuromotor/neurosensory function. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and performance on tests of neuromotor or neurosensory function (Table 2-32). The largest study analyzed data from NHANES III (1988–1994) and found no association ($p=0.34$) between concurrent PbB and simple visual reaction time in a cohort of 5,700 adults (age 20–50 years; Krieg et al. 2005). The geometric mean PbB was 2.51 $\mu\text{g/dL}$ (range 0.7–42) and 96% of the cohort was < 10 $\mu\text{g/dL}$. A more recent analysis of data from NHANES (1999–2002) examined walking speed in cohorts of approximately 1,800 males or females and found a significant association between increasing PbB and decreasing walking speed in females in a PbB stratum $2.2\text{--}\leq 2.9$ $\mu\text{g/dL}$ compared to < 1.6 $\mu\text{g/dL}$; there was a significant trend with increasing PbB (Ji et al. 2013). This outcome is consistent with a smaller cross-sectional study of women (mean age 70 ± 4 years) that found significant decreases in upper and lower extremity reaction times in association with increasing PbB (Muldoon et al.

1996). A longitudinal study of a cohort from the Normative Aging Study found no significant associations between bone or blood Pb and hand tremor in males (mean age 60 ± 7 years; Ji et al. 2015). The mean PbB for the cohort was 5.0 ± 2.7 (SD) $\mu\text{g/dL}$. A longitudinal study of males ($n=1,188$), age range 50–86 years, conducted in Germany, found associations between increasing PbB and decreasing performance scores on tests of dexterity (Casjens et al. 2018). The median PbBs were $3.29 \mu\text{g/dL}$ at the start of the study ($2.27\% > 9 \mu\text{g/dL}$) and $2.29 \mu\text{g/dL}$ ($0.84\% > 9 \mu\text{g/dL}$) at the 11-year follow-up. This study examined several metrics of dexterity (finger tapping and aiming, line tracing, steadiness). The association with Pb was strongest for the finger tapping test. The OR for impaired performance on the finger tapping test at the follow-up was 2.63 (95% CI: 1.26, 5.94) for the PbB stratum $5.0 < 9 \mu\text{g/dL}$ and 0.80 (95% CI: 0.14, 4.59) for the PbB stratum $> 9 \mu\text{g/dL}$.

Several studies have examined associations between PbB and sensory function in adults, including olfaction (Casjens et al. 2018) and hearing (Huh et al. 2018; Hwang et al. 2009; Kang et al. 2018). Two studies examined association between PbB and hearing using data from the Korean National Health and Nutrition Examination Study (KNHANES) (Huh et al. 2018; Kang et al. 2018). Both studies found associations between increasing PbB and high-frequency hearing loss. The larger of the two studies ($n=6,409$) estimated ORs for high-frequency hearing loss in females and males in the age range 19–85 years. The ORs were 1.629 (95% CI: 1.161, 2.287) in the highest male PbB quartile (mean PbB: $4.2 \mu\text{g/dL} \pm 0.04$ SE) and 1.502 (95% CI: 1.027, 2.196) in the highest female PbB quartile (mean PbB: $3.03 \mu\text{g/dL} \pm 0.03$ SE). A smaller cross-sectional study of steel workers ($n=259$) also found associations between increasing PbB and hearing loss that extended from 3,000 to 8,000 Hz in the PbB stratum $\geq 7 \mu\text{g/dL}$ (Hwang et al. 2009). Performance on an odor identification test was not associated with PbB in a longitudinal study of males ($n=1,188$), age range 50–86 years (Casjens et al. 2018).

Neurological diseases. Possible associations between Pb exposure and risk of ALS have been examined in case-control studies (Fang et al. 2010; Kamel et al. 2002). A case-control study of 184 male ALS cases and 194 matched controls found a significant association between increasing PbB and ALS (Fang et al. 2010). The mean PbB for cases was $2.41 \mu\text{g/dL}$ (range 0.72 – $7.58 \mu\text{g/dL}$). A case-control study of 109 ALS cases (43 females, 66 males) and 194 matched controls estimated the OR for ALS to be 1.9 (95% CI: 1.4, 2.6) for a $1 \mu\text{g/dL}$ increase in PbB (Kamel et al. 2002).

Associations Between Bone Pb and Neurological Effects in Adults. Decrements in neurological function in adults have also been associated with bone Pb (Table 2-33). In general, these studies provide further support for associations between Pb exposure and neurobehavioral function, including decrements

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in cognitive function, altered neuromotor and neurosensory function, and altered behavior and mood. Most of these studies are of cohorts from longitudinal health studies: Boston Memory Study (Bandeem-Roche et al. 2009; Glass et al. 2009; Shih et al. 2006), Nurses' Health Study (Power et al. 2014; Weuve et al. 2009), or Normative Aging Study (Eum et al. 2013; Farooqui et al. 2017; Grashow et al. 2013a, 2013b, 2015; Ji et al. 2015; Park et al. 2010; Payton et al. 1998; Power et al. 2014; Rajan et al. 2007, 2008; Rhodes et al. 2003; Schwartz et al. 2005; Wang et al. 2007, 2018; Weisskopf et al. 2004, 2007; Wright et al. 2003b). These studies have provided both cross-sectional and longitudinal assessments of associations between bone Pb (and PbB) and neurological function in adult populations. Longitudinal designs are particularly important because they allow age-related declines in cognitive function to be assessed. Longitudinal studies have found that associations between bone Pb and cognitive function (learning, memory) persist when adjustments are made for age (Bandeem-Roche et al. 2009; Dorsey et al. 2006; Eum et al. 2013; Grashow et al. 2013a; Khalil et al. 2009; Payton et al. 1998; Power et al. 2014; Rajan et al. 2008; Schwartz et al. 2005; Seegal et al. 2013; Shih et al. 2006; Stewart et al. 2002; van Wijngaarden et al. 2009; Weisskopf et al. 2007; Weuve et al. 2009, 2013; Wright et al. 2003b). Rates of decrement in cognitive function with age have been found to be more severe in association with increasing bone Pb (Farooqui et al. 2017; Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Bandeem-Roche et al. 2009	965 adults, age: 50–70 years ^a	↑ T	–	–	Learning, memory, executive function, eye-hand coordination
Coon et al. 2006	121 adult cases, 414 controls, age: 50–>80 years	–	↑ 0 ^d	–	Parkinson's disease
Dorsey et al. 2006	652 adult Pb workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function, manual dexterity, vibration threshold, depression

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Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Eum et al. 2013	789 adult males ^b , age: 68 years (median)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function
Eum et al. 2015	100 adult cases, 194 controls, age: 60 years (mean)	–	↑ P ↑ T	–	Interaction between Pb, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms
Farooqui et al. 2017	741 males, age: 68 years (mean)	↑ P 0 T	–	–	Memory, visuospatial ability, attention, language, orientation
Glass et al. 2009	1,001 adults ^a , age: 50–70 years	↑ T	↑ T	–	Interaction between Pb and psychosocial hazard scale for eye-hand coordination, executive function, language
Grashow et al. 2013a	51 adult males ^b , age: 75 years (mean)	↑ P 0 T	–	–	Fear conditioning
Grashow et al. 2013b	362 adult males ^b , age: 69 years (mean)	–	↑ P ↑ T	–	Manual dexterity
Grashow et al. 2015	164 adult males ^b , age: 80 years (mean)	–	0 P ↑ T	–	Olfactory function
Ji et al. 2015	672 adult males ^b , age: 50–98 years	–	0 P 0 T	–	Tremor (no association in adjusted models)
Kamel et al. 2002	109 adult cases, 256 controls, age: 30–80 years	–	0 P 0 T	–	Amyotrophic lateral sclerosis (no association in adjusted models)
Khalil et al. 2009	83 adult workers and 51 controls, age: >55 years	↑ T	–	–	Learning, memory

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Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Park et al. 2010	448 adult males ^b , age: 65 years (mean)	–	↑ P ↑ T	–	Hearing function
Payton et al. 1998	141 adult males ^b , age: 67 years (mean)	↑ T	–	–	Memory, visual-spatial performance
Power et al. 2014	584 adult females ^c , age: 60–74 years	0 P 0 T	–	–	Learning, memory, executive function
Rajan et al. 2007	1,075 adult males ^b , age: 48–94 years	–	–	↑ P ↑ T	Psychiatric symptoms
Rajan et al. 2008	982 adult males ^b , age: 49–72 years	0 P ↑ T	–	–	Visual-spatial performance
Rhodes et al. 2003	536 adult males ^b , age: 48–70 years	–	–	↑ P ↑ T	Anxiety
Schwartz et al. 2000b	535 Pb workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed Pb workers and 135 controls, age: 40 years (mean)	0 T	0 T	0 T	Learning, memory, executive function, manual dexterity, grip strength, mood and depression
Schwartz et al. 2005	576 exposed Pb workers, age: 41 years (mean)	↑ T	↑ T	↑ T	Executive function, manual dexterity, vibration threshold, depression
Seegal et al. 2013	241 capacitor workers, age: 64 years (mean)	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity
Shih et al. 2006	991 adults ^a , age: 50–70 years	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity

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Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Stewart et al. 2002	529 Pb workers, age: 40–>70 years	↑ T	↑ T	–	Learning, memory, executive function, reaction time, manual dexterity
van Wijngaarden et al. 2009	47 adults, age: 55–67 years	↑ C	–	–	Learning, memory
Wang et al. 2007	358 adult males ^b , age: 67 years (median)	↑ T	–	–	Interaction between Pb and hemochromatosis gene polymorphisms on learning, memory, executive function
Wang et al. 2018	634 males, age: 67 years (mean)	–	↑ P ↑ T	–	Glaucoma
Weisskopf et al. 2004	466 adult males ^b , age: 68 years (mean)	↑ P	–	–	Memory, verbal and written skills, executive function
Weisskopf et al. 2007	761 adult males ^b , age: 69 years (mean)	↑ P ↑ T	–	–	Memory, visual-spatial performance
Weisskopf et al. 2010	330 adult cases and 308 controls, age: 67 years (mean)	–	↑ T	–	Parkinson's disease
Weuve et al. 2009	587 adult females ^c , age: 47–74 years	0 P ↑ T	–	–	Learning, memory
Weuve et al. 2013	101 cases and 50 controls, age: 55–80 years	0 P ↑ T	–	–	Learning, memory (stronger association with Pb among Parkinson's disease cases)

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Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Wright et al. 2003b	736 adult males ^b , age: 68 years (mean)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function

^aBoston Memory Study.^bNormative Aging Study.^cNurses Health Study.^dWhole-body Pb predicted from bone Pb.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; C = calcaneus bone; P = patella; Pb = lead; T = tibia; O = other

Bone Pb has been associated with declines in neuromotor and neurosensory function. Neuromotor outcomes that have been associated with bone Pb include tremor, Parkinson's disease, and ALS (Coon et al. 2006; Eum et al. 2015; Weisskopf et al. 2010; Weuve et al. 2013). Neurosensory outcomes include decrements in olfactory and hearing function, vibration threshold, and manual dexterity (Dorsey et al. 2006; Grashow et al. 2013b, 2015; Park et al. 2010; Schwartz et al. 2000b, 2005; Shih et al. 2006; Stewart et al. 2002). Bone Pb has also been associated with increased risk or odds of psychiatric symptoms such as anxiety and depression (Dorsey et al. 2006; Rajan et al. 2007; Rhodes et al. 2003; Schwartz et al. 2005).

Mechanisms of Action. Numerous cellular mechanisms are likely involved in Pb-induced alterations in neurological function. Pb disrupts cellular function through diverse mechanisms, including displacement of metal ion co-factors from protein, enzyme inhibition, inhibition of ion transport, disruption of cell and mitochondrial membrane potentials, disruption of intracellular calcium homeostasis oxidative stress, and inflammation and endocrine disruption (see Section 2.21). All of these Pb mechanisms have been demonstrated in neuronal tissues, although there is no consensus on which mechanisms dominate. Evidence for various mechanisms that may participate in Pb neurotoxicity are summarized in this section. The reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; EPA 2014c; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Mitra et al. 2017; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000; Zhang et al. 2015).

Pb can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by Pb. One pathway that has been studied in more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ -isoform is one of several calcium-dependent forms of PKC and is a likely target for Pb neurotoxicity; it is neuron-specific and is involved in long-term potentiation (see below), spatial learning, and memory processes. Pb has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of Pb can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of Pb activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low Pb levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for Pb PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by Pb via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes, along with endothelial cells, make up the blood-brain barrier. Studies in rats exposed chronically to low Pb levels have reported alterations in the normal pattern of GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to Pb. An inhibition of microvascular formation has been observed with Pb concentrations that are effective in activating PKC. Thus, it appears that premature activation of PKC by Pb may impair brain microvascular formation and function, and at high levels of Pb exposure, may account for gross defects in the blood-brain barrier that contribute to acute Pb encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain, and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. The particular vulnerability of the fetus and infant to the neurotoxicity of Pb may be due in part to

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immature brain microvessels, which affect the blood brain barrier, and to the lack of the high-affinity Pb-binding protein in astroglia, which sequester Pb.

Another enzyme altered by Pb is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; Pb improperly activates the enzyme. Some studies suggest that activation of calmodulin by Pb results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of Pb on gene expression via activation of calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more Pb than activation of PKC.

Pb also can substitute for zinc in some enzymes and in zinc-finger proteins, which coordinate one or more zinc cations as cofactors. The substitution of Pb for zinc in zinc-finger proteins can have significant effects on *de novo* expression of the bound proteins and in any genes transcriptionally-regulated by a particular protein. Pb has been found to alter the binding of zinc-finger transcriptional regulator Sp1 to its specific DNA sequences. This is accompanied by aberrant expression of Sp1 target genes such as myelin basic protein and proteolipid protein. Another gene regulated by Sp1 is the β -amyloid precursor protein (APP) gene. Recently, it was shown that Pb exposure in neonatal rats transiently induces APP mRNA, which is overexpressed with a delay of 20 months after exposure to Pb has ceased. In contrast, APP expression, and Sp1 activity, as well as APP and β -amyloid protein levels, were unresponsive to Pb during old age, suggesting that exposures occurring during brain development may predetermine the expression and regulation of APP later in life. It has been suggested that the multiple responses to Pb exposure are due to Pb specifically targeting zinc-finger proteins found in enzymes, channels, and receptors.

Pb affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, cholinergic, and gamma-aminobutyric acid (GABA) systems. Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has

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been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to Pb diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of Pb on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Pb exposure inhibits release of glutamine from pre-synaptic endings, which may be mediated, in part, by altered pre-synaptic vesicle formation or activation. Studies have shown that the effects of Pb vary as a function of the developmental exposure period and that Pb exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by Pb during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing Pb doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

Studies in animals treated with Pb (PbB 30–40 µg/dL) have shown that induction of pair-pulse facilitation in the dentate gyrus is impaired. Since the phenomenon is mediated primarily by increased glutamate release, the reasonable assumption is that Pb reduces glutamate release. Support for this assumption is also derived from studies in which depolarization-induced hippocampal glutamate release was reduced in awake animals with similar PbB. This inhibition of glutamate release was shown to be due to Pb-related decrements in a calcium-dependent component. The exact mechanism for the inhibition of glutamate release by Pb is not known, but is consistent with Pb at nanomolar concentrations preventing maximal activation of PKC, rather than Pb blocking calcium influx into the presynaptic terminal through voltage-gated calcium channels. Reduced glutamate release has been observed in rats exposed from conception through weaning and tested as adults, when Pb was no longer present, suggesting that a direct action of Pb is not necessary and that other mechanisms, such as reductions in synaptogenesis, also may be involved. As with LTP, depolarization-evoked hippocampal glutamate release in rats treated chronically with several dose levels of Pb exhibited a U-shaped response. That is, glutamate release was inhibited in rats treated with the lower Pb doses, but not in those exposed to the higher concentrations of Pb. Although speculative, this was interpreted as Pb at the higher doses mimicking calcium in promoting transmitter release and overriding the inhibitory effects of Pb that occur at lower Pb levels.

The findings regarding the effects of Pb on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of Pb on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats

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from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 µg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a Pb-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson's disease, a disease associated with dopamine depletion in the striatum, sometimes show difficulties in cognitive functions. Most of the evidence available suggests that Pb may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of Pb on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to Pb resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus accumbens (a terminal dopamine projection area) and the frontal cortex resulted in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of Pb. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of Pb on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to Pb. This type of change has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to Pb induces numerous changes in cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that Pb blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that Pb reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, Pb prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that Pb can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether Pb alters the

expression of nicotinic cholinergic receptors in the developing brain. Evidence for an involvement in Pb-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal Pb treatment of rats. Chronic exposure of rats to Pb has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not Pb exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that Pb does not directly affect muscarinic receptors with the exception of the visual cortex, where Pb may have a direct inhibitory effect on muscarinic receptors from rods and bipolar cells of the retina.

Pb exposure decreases spontaneous and evoked release of GABA in rats and in hippocampal cultures and brain slices. In general, GABA functions in the brain as a post-synaptic inhibitory transmitter. The role of changes in GABA release in the neurotoxicity of Pb has not been firmly established.

Various other mechanisms may also contribute to Pb neurotoxicity. Exposure to Pb has also been shown to stimulate inflammation in a variety of tissues, including neuronal tissue (see Section 2.21).

Contributing mechanisms include alterations in levels of ROS, activation of nuclear activation factor NF κ B, cytokine release, and alterations in prostaglandin metabolism. Pb exposure has been shown to alter neuronal nitric oxide signaling (NOS) and the hormone levels regulated by the hypothalamic-pituitary-thyroid axis.

2.17 REPRODUCTIVE

Overview. Numerous epidemiological studies have evaluated effects of Pb on male and female reproductive function. In males, most exposures were occupational, with mean PbB >10 μ g/dL. In general, studies in males show consistent evidence of reproductive effects on sperm (production, motility, viability, and morphology), semen quantity and composition, serum reproductive hormone levels, and fertility, with severity of effects increasing with increasing PbB. In contrast to exposure of males, most exposures of females were non-occupational, with mean PbB \leq 10 μ g/dL. Studies investigating effects on serum reproductive hormone levels, fertility, spontaneous abortion, and preterm birth provide mixed results; thus, dose-dependence of effects in females is difficult to assess.

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The following reproductive effects in males have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Increased serum testosterone; evaluated in a few studies with mixed results.
 - Effects on sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); evaluated in a few studies with mixed results.
- > 10 $\mu\text{g/dL}$:
 - Altered serum concentrations of reproductive hormones (testosterone, FSH, LH); evaluated in several studies with mixed results.
 - Effects on sperm (decreased sperm count, concentration, motility, viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); corroborated in several studies.
 - Alterations in semen quality (decreased semen volume and altered composition of seminal fluid); evaluated in a few studies.
 - Decreased fertility; evaluated in a few studies.
 - Histopathological changes to the testes (peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells); evaluated in a few studies.

The following reproductive effects in females have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Increased serum levels of estradiol, FSH, and LH; studies have mixed results.
 - Decreased fertility; studies have mixed results.
 - Increased spontaneous abortion; studies have mixed results.
 - Increased preterm birth; studies have mixed results.
 - Earlier age at onset of menopause; demonstrated in a few studies.
- > 10 $\mu\text{g/dL}$:
 - Decreased fertility; studies have mixed results.
 - Increased preterm birth; studies have mixed results.

Measures of Exposure. Most studies evaluating effects on male and female reproductive systems used PbB as the biomarker for exposure. More recent studies in men have explored the relationship between the concentration of Pb in semen or spermatozoa and adverse effects (Table 2-34). It has been suggested

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that semen levels of Pb may be a better biomarker for assessment of male reproductive effects, particularly at low PbB, because no relationship between PbB and Pb levels in semen or spermatozoa has been observed (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011). In women, other biomarkers of exposure include concentration of Pb in plasma (Lamadrid-Figueroa et al. 2007), red blood cells (Perkins et al. 2014), placenta (Gundacker et al. 2010), and plasma/blood ratio (Lamadrid-Figueroa et al. 2007).

Confounding Factors and Effect Modifiers. Numerous factors may add uncertainty in the interpretation of studies examining associations between PbB and reproductive effects, including overall health, body weight, nutrition, and SES. Exposures to other substances, including recreational drugs, alcohol, therapeutic agents, industrial chemicals, insecticides, and pesticides, also may affect fertility (Foster and Gray 2008). Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome. Some studies examining effects on sperm (discussed below) were conducted on samples obtained at fertility clinics; therefore, other causes for sperm effects could be effect modifiers (additional details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 11). In addition, because sperm counts can vary by geographical location, it is important that control and exposed groups are matched for geographic location.

Characterization of Effects in Males. General trends regarding the relationship between PbB and male reproductive effects are shown in Table 2-34. Overall, the dose-effect pattern suggests an increasing severity of toxicity associated with increasing PbB, with effects on sperm at ≤ 10 $\mu\text{g/dL}$ (discussed in more detail below). At increasing PbB, effects become more severe, with decreased fertility observed at $\text{PbB} > 10$ $\mu\text{g/dL}$ and histopathological changes of the testes at PbB of approximately 30 $\mu\text{g/dL}$. Effects on sperm, including decreased sperm count, concentration, motility, viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm, have been observed at PbB of ≤ 10 – > 50 $\mu\text{g/dL}$ (Alexander et al. 1998a; Assennato et al. 1987; Bonde et al. 2002; Cullen et al. 1984; Famurewa and Ugwuja 2017; Hernández-Ochoa et al. 2005; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Li et al. 2015; Meeker et al. 2008; Moran-Martinez et al. 2013; Telisman et al. 2007; Wildt et al. 1983). However, a few studies showed no association between PbB and adverse effects on sperm (Lancranjan et al. 1975; Mendiola et al. 2011). The significance of the observed changes to sperm on fertility is uncertain. Decreased semen volume and altered composition of seminal fluid have been observed at $\text{PbB} > 10$ $\mu\text{g/dL}$ (Bonde et al. 2002; Naha and Chowdhury 2006; Telisman et al. 2000; Wildt et al. 1983). Decreased fertility has been reported in association with $\text{PbB} > 10$ – > 50 $\mu\text{g/dL}$ (Sallmén et al. 2000; Shiau et al. 2004), although no effect on fertility was observed in one study of workers with PbB

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>40 µg/dL (Coste et al. 1991). Histopathological assessment of biopsied testicular tissue from Pb workers (mean PbB: 29.0 µg/dL) showed peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells (Braunstein et al. 1978). Evaluations of associations between PbB and serum levels of reproductive hormones show inconsistent results (Table 2-35). At PbB ≤10 µg/dL, positive associations between PbB and serum testosterone levels have been observed (Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007), whereas inverse associations or no effects were reported at PbB >10 µg/dL. No effects on FSH or LH were reported at PbB ≤10 µg/dL, and inconsistent results were observed at PbB >10 µg/dL. Changes in serum levels of reproductive hormones may indicate disruption of the hypothalamic-pituitary-gonadal axis; however, due to inconsistent findings, an association between PbB and endocrine disruption in males has not been firmly established.

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Effects on sperm (decreased sperm concentration, motility, and viability; increased morphologic abnormalities)	Famurewa and Ugwuja 2017; Hernández-Ochoa et al. 2005; Li et al. 2015; Meeker et al. 2008; Telisman et al. 2007
	Effects on hormones (increased serum levels of testosterone, estradiol, LH, FSH, and SHBG; decreased serum prolactin and SHBG)	Chen et al. 2016; Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007
>10–30	Effects on sperm (decreased sperm count, concentration, density, motility, viability; morphologic abnormalities)	Alexander et al. 1998a; Bonde et al. 2002; Moran-Martinez et al. 2013
	Effects on semen (decreased volume)	Bonde et al. 2002
	Decreased fertility	Sallmén et al. 2000
>30–50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Hsu et al. 2009; Lancranjan et al. 1975; Lerda 1992; Telisman et al. 2000
	Effects on composition of seminal fluid	Telisman et al. 2000
	Effects on hormones (increased estradiol, LH, FSH; decreased testosterone)	Braunstein et al. 1978; Ng et al. 1991; Telisman et al. 2000
	Histopathological changes to testes (peritubular fibrosis, oligospermia, vacuolization of Sertoli cells)	Braunstein et al. 1978
	Decreased fertility	Sallmén et al. 2000; Shiau et al. 2004

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Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Assennato et al. 1987; Cullen et al. 1984; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on semen (decreased volume; altered composition)	Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on hormones (altered serum levels of testosterone, FSH, LH, prolactin)	Assennato et al. 1987; Rodamilans et al. 1988
	Decreased fertility	Sallmén et al. 2000

FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone binding globulin

Table 2-35. Effects on Reproductive Hormones Associated with Chronic Exposure to Lead (Pb) in Males

PbB (µg/dL)	Hormone							Reference
	T	FSH	LH	E	P	A	SHBG	
≤10	↑	0	–	–	–	0	0	Kresovich et al. 2015
	↑	0	0	–	–	–	0	Meeker et al. 2010
	↑	–	–	↑	0	–	–	Telisman et al. 2007
	↑	–	–	–	–	–	–	Lewis and Meeker 2015
	↑	↑	↑	0	–	–	↑	Chen et al. 2016
	0	0	0	–	–	–	–	Mendiola et al. 2011
10–30	0	0	0	–	–	–	–	Hsieh et al. 2009
	0	0	0	–	–	–	–	Alexander et al. 1998a
30–50	↓	0	0	–	0	–	–	Braunstein et al. 1978
	0	0	0	–	0	–	–	Erfurth et al. 2001
	0	↓	↓	–	–	–	–	Gustafson et al. 1989
	0	↑	↑	–	–	–	–	McGregor and Mason 1990
	↓	↑	↑	–	0	–	–	Ng et al. 1991
	–	–	–	↑	–	–	–	Telisman et al. 2000
	0	0	0	0	–	–	–	Sadeghnaiit Haghighi et al. 2013
	↓	–	–	–	–	–	–	Rodamilans et al. 1988

0 = no effect; ↑ = increased serum level; ↓ = decreased serum level; – = not evaluated; A = androstenedione; E = estradiol; FSH = follicle stimulating hormone; LH = luteinizing hormone; P = prolactin; SHBG = sex hormone binding globulin; T = testosterone

Effects in Males at Blood Pb Levels ≤ 10 $\mu\text{g}/\text{dL}$. Cross-sectional studies evaluating adverse effects of non-occupational exposures to Pb on the male reproductive system show that damage to sperm, decreased semen volume, and increased serum testosterone are associated with mean PbB ≤ 10 $\mu\text{g}/\text{dL}$ or with Pb concentrations in semen or spermatozoa when PbBs are ≤ 10 $\mu\text{g}/\text{dL}$. Results are summarized in Table 2-36, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 11. None of the studies evaluated associations between PbB and male fertility parameters (i.e., pregnancy). Three studies assessed larger populations, including two studies using NHANES data (Kresovich et al. 2015; Lewis and Meeker 2015) and one study of a Chinese population (Chen et al. 2016). However, in general, study populations were small ($n=61$ – 240). In addition, for a few studies, participants were selected from infertility clinics and it is unclear how this may have biased study results (Meeker et al. 2008, 2010; Mendiola et al. 2011). Despite these limitations, taken together, results of non-occupational exposure studies support that adverse effects to the male reproductive system occur at PbB ≤ 10 $\mu\text{g}/\text{L}$.

Sperm and semen. A significant association between an increase in PbB ≤ 10 $\mu\text{g}/\text{dL}$ and increasing percentages of morphologically abnormal sperm, wide sperm, and round sperm was observed in a population of Croatian men (Telisman et al. 2007). The mean PbB was 4.92 $\mu\text{g}/\text{dL}$; although the maximum PbB value in this study was 14.9 $\mu\text{g}/\text{dL}$, over 90% of participants had PbB < 10 $\mu\text{g}/\text{dL}$. Li et al. (2015) found small, but significant inverse associations between PbB and sperm count, sperm concentration, motile sperm, and morphologically normal sperm in 154 men from a reproductive clinic in Taiwan. The median PbB was 2.78 $\mu\text{g}/\text{dL}$ (SD 1.85); range and percentiles were not reported. Sperm count was associated with PbB in a small population of infertile men with mean PbB 1.71–2.05 $\mu\text{g}/\text{dL}$ (Famurewa and Ugwuja 2017). Other studies have shown associations between Pb levels in semen and/or spermatozoa and increased percentages of morphologically abnormal sperm and decreased sperm motility and viability, although no associations were observed between PbB and these outcomes (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011); mean PbB levels were 9.3 $\mu\text{g}/\text{dL}$ in the Hernandez-Ochoa et al. (2005) study and 2.8 $\mu\text{g}/\text{dL}$ in the Mendiola et al. (2011) study. No associations were observed between PbB and sperm concentration, motility, or morphologic abnormalities in men at a median PbB of 1.5 $\mu\text{g}/\text{dL}$ (Meeker et al. 2008). Semen volume (mL) was inversely associated with PbB at a mean PbB of 9.3 $\mu\text{g}/\text{dL}$; however, 48% of participants had PbB > 10 $\mu\text{g}/\text{dL}$ (Hernandez-Ochoa et al. 2005).

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Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}^a$

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Effects on serum hormone levels			
Chen et al. 2016	Median (IQR): 4.40 (2.90–6.23)	Testosterone	β coefficient (SE) Q4: 0.033 (0.010); $p < 0.01^*$
Cross-sectional study; n=2,286	Quartiles: • Q1: < 2.9 (n=558) • Q2: 2.9–4.39 (n=572) • Q3: 4.4–6.2 (n=585) • Q4: > 6.2 (n=571)	FSH	β coefficient (SE) Q4: 0.030 (0.015); $p < 0.05^*$
		LH	β coefficient (SE) Q4: 0.028 (0.013); $p < 0.05^*$
		E	β coefficient (SE) Q4: -0.003 (0.017)
		SHBG	β coefficient (SE) Q4: 0.038 (0.012); $p < 0.01^*$
Kresovich et al. 2015	Median: 2.0	Testosterone	β coefficient ng/mL per $\mu\text{g/dL}$ (SE)
Cross-sectional study; n=869	Quartiles: • Q1: ≤ 1.4 (reference) • Q2: 1.4–2.1 • Q3: 2.10–3.20 • Q4: > 3.20		• Q3: 0.54 (0.21); $p < 0.05^*$
			• Q4: 0.79 (0.22); $p < 0.05^*$;
			p-trend=0.00268*
Lewis and Meeker 2015	Gmean: 1.06	Testosterone	• Percent change in serum testosterone concentration associated with a doubling (100% increase) in PbB: 6.65% (2.09, 11.41); $p < 0.004^*$; p-trend across quartiles=0.003*
Cross-sectional study; n=484	Quartiles: • Q1: < 0.71 • Q2: 0.71–1.00 • Q3: 1.00–1.59 • Q4: 1.59–33.67		

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Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}^a$

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Meeker et al. 2010	Median: 1.5 Quartiles	Testosterone	Regression coefficient Q4 (ng/dL per µg/dL): 39.9 (3.32, 76.4)*
Cross-sectional study; n=219	• Q1: <1.1 (reference)	FSH	Regression coefficient Q4 (mIU/mL per µg/dL): 0.07 (-0.18, 0.31)
	• Q2: 1.1–1.5	LH	Regression coefficient Q4 (mIU/m per µg/dL): 0.08 (-0.14, 0.29)
	• Q3: 1.5–2.0	Inhibin B	Regression coefficient Q4 (pg/mL per µg/dL): -7.79 (-29.0, 13.4)
	• Q4: >2.0–16.2	SHBG	Regression coefficient Q4 (nmol/L per µg/dL): 0.07 (-0.10, 0.23)
Mendiola et al. 2011	Gmean: 2.8	FAI	Regression coefficient Q4 (per µg/dL): 0.08 (-0.05, 0.21)
		Testosterone	β coefficient (ng/mL per µg/L): -0.12 (-0.40, 0.14)
		FSH	β coefficient (IU/L per µg/L): -0.20 (-0.64, 0.25)
		LH	β coefficient (IU/L per µg/L): -0.07 (-0.49, 0.31)
Telisman et al. 2007	Median: 4.92	Testosterone	β coefficient (nmol/L per µg/L): 0.21; p<0.003*
Cross-sectional study; n=240		Estradiol	β coefficient (nmol/L per µg/L): 0.22; p<0.0008*
		Prolactin	β coefficient (µg per µg/L): -0.18; p<0.007
Sperm and semen quality			
Famurewa and Ugwuja 2017	PbB: Mean	Semen volume	Pearson correlation R value: -0.132; p=0.27
Cross-sectional study; n=75 men with infertility	• Normospermic: 1.49 • Azospermic: 1.71 • Oligospermic: 2.05	Sperm count	Pearson correlation R value: -0.280; p=0.02*
		Sperm motility	Pearson correlation R value: -0.092; p=0.44
		Sperm morphology	Pearson correlation R value: -0.081; p=0.50

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Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}^a$

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Hernandez-Ochoa et al. 2005	Mean: 9.3 SPZ Pb: 0.047 ng/10 ⁶ cells SF Pb: 2.02 $\mu\text{g/L}$	Log sperm concentration	β coefficient SPZ Pb (10 ⁶ cells/mL per ng/10 ⁶ cells): -17.17 (p<0.05)*
Cross-sectional study; n=68		Sperm motility	β coefficient PbB (% per $\mu\text{g/dL}$): -0.006 β coefficient SPZ Pb (% per ng/10 ⁶ cells): -2.12 (p<0.05)*
		Sperm morphology (abnormal)	β coefficient PbB (% per $\mu\text{g/dL}$): -0.001 β coefficient SPZ Pb (% per ng/10 ⁶ cells): -1.42 (p<0.05)*
		Sperm viability	β coefficient PbB (% per $\mu\text{g/dL}$): -0.095 β coefficient SPZ Pb (% per ng/10 ⁶ cells): -0.130 (p<0.05)*
		Semen volume	β coefficient PbB (mL per $\mu\text{g/dL}$): -0.043 β coefficient SF Pb (mL per $\mu\text{g/L}$): -0.183 mL; p<0.05*
Li et al. 2015	Mean: All participants: 2.78 Low-quality semen group: 3.43 High-quality semen group: 2.38	Low quality sperm	OR: 1.040 (1.011, 1.069); p=0.0061*
Cross-sectional study; n=154		Decreased sperm concentration	OR: 1.046 (1.015, 1.078); p=0.0032*
		Decreased sperm number	OR: 1.041 (1.012, 1.071); p=0.0048*
		Decreased motile sperm	OR: 1.057 (1.026, 1.089); p=0.0003*
		Decreased morphologically normal sperm	OR: 1.071 (1.025, 1.118); p=0.0021*
Meeker et al. 2008	Median: 1.50 • Quartiles (Q): ○ Q1: <1.10 ○ Q2: 1.10–1.50 ○ Q3: 1.50–2.00 ○ Q4: 2.00–16.2	Sperm concentration	Regression coefficient (10 ⁶ /mL per $\mu\text{g/dL}$) Q4: 0.02 (-0.39, 0.43)
Cross-sectional study; n=219		Sperm motility	Regression coefficient (% per $\mu\text{g/dL}$) Q4: 1.10 (-4.56, 6.75)
		Sperm morphology	Regression coefficient (% per $\mu\text{g/dL}$) Q4: -0.16 (-1.58, 1.26)
		Semen volume	Regression coefficient (mL per $\mu\text{g/dL}$) Q4: 0.17 (-0.41, 0.74)

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Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Mendiola et al. 2011	Gmean: 2.8 Median: 2.9	Sperm concentration	β coefficient (10 ⁶ /mL per µg/L): 0.08 (-4.1, 5.2)
Case-control study; n=61		Immobile sperm	β coefficient (% per µg/L): -0.49 (-1.8, 0.62)
		morphologically normal sperm	β coefficient(% per µg/L): -0.8 (-3.5, 3.4)
Telisman et al. 2007	Median: 4.92	Immature sperm	β coefficient (10 ⁶ /mL per µg/L): 0.13 (p<0.07)
Cross-sectional study; n=240		Pathologic sperm	β coefficient (% per µg/L): 0.31 (p<0.0002)*
		Wide sperm	β coefficient (% per µg/L): 0.32 (p<0.0001)*
		Round sperm	β coefficient (% per µ: 0.16 (p<0.03)*

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 11 for more detailed descriptions of studies.

^bParticipants had no known occupational exposure to Pb.

^cAsterisk and bold indicate association with PB; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

CI = confidence interval; E = estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; Gmean = geometric mean; Inhibin B = gonadal dimeric polypeptide hormone; IQR = interquartile range; LH = luteinizing hormone; OR = odds ratio; Pb = lead; SE = standard error; SF = seminal fluid; SHBG = sex hormone-binding globulin; SPZ = spermatozoa

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Serum testosterone levels. Significant associations have also been observed between PbB ≤ 10 $\mu\text{g/dL}$ and increased serum testosterone levels (Table 2-34). Studies using NHANES data found significant positive associations between PbB and serum testosterone levels (Kresovich et al. 2015; Lewis and Meeker 2015). Examined by PbB quartiles, Kresovich et al. (2015) observed significant positive associations between PbB and serum testosterone (ng/L) for PbBs of 2.10–3.20 and >3.2 $\mu\text{g/dL}$; the median PbB of the study population was 2.0 $\mu\text{g/dL}$. A doubling of PbB was positively associated with a 6.65% change in serum testosterone; the mean PbB of the study population was 1.06 $\mu\text{g/dL}$ (Lewis and Meeker 2015). The toxicological significance of the observed associations between PbB and serum testosterone has not been established.

Characterization of Effects in Females. As noted above, most epidemiological studies evaluated effects at PbB ≤ 10 $\mu\text{g/dL}$, with few studies of PbB >10 $\mu\text{g/dL}$. Studies of PbB ≤ 10 $\mu\text{g/dL}$ are discussed in detail in the section below. General trends for studies showing a relationship between PbB ≤ 10 –50 $\mu\text{g/dL}$ and female reproductive effects are shown in Table 2-37. Effects associated with PbB include increased serum levels of estradiol, FSH, and LH at PbB ≤ 10 $\mu\text{g/dL}$ (Chang et al. 2006; Krieg 2007), decreased fertility at PbB ≤ 10 $\mu\text{g/dL}$ (Chang et al. 2006), increased time to pregnancy at PbB >30 –40 $\mu\text{g/dL}$ (Sallmén et al. 1995), increased spontaneous abortion at PbB ≤ 10 –30 $\mu\text{g/dL}$ (Borja-Aburto et al. 1999; Yin et al. 2008), decreased number of gestational days at PbB >10 –40 $\mu\text{g/dL}$ (Jelliffe-Pawlowski et al. 2006), and increased preterm birth at PbB ≤ 10 –50 $\mu\text{g/dL}$ (McMichael et al. 1986; Jelliffe-Pawlowski et al. 2006; Rabito et al. 2014). Although epidemiological studies demonstrate effects on reproductive function, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects (Baghurst et al. 1987; Bloom et al. 2010, 2011, 2015; Garcia-Esquinas et al. 2014; Jackson et al. 2007; Murphy et al. 1990; Perkins et al. 2014; Pollack et al. 2011; Sallmén et al. 1995; Taylor et al. 2015; Vigeh et al. 2010). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤ 10 $\mu\text{g/dL}$) in most studies.

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Table 2-37. Overview of Effects on the Female Reproductive System and Pregnancy Outcomes Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased serum hormones (estradiol, FSH, LH) Decreased fertility Increased spontaneous abortion Increased preterm birth Earlier age at menopause	Chang et al. 2006; Chen et al. 2016; Krieg 2007 Chang et al. 2006 Yin et al. 2008 Li et al. 2017b; Rabito et al. 2014 Eum et al. 2014; Popovic et al. 2005
>10–30	Increased spontaneous abortion Decreased number of gestational days Increased preterm birth	Borja-Aburto et al. 1999 Jelliffe-Pawlowski et al. 2006 McMichael et al. 1986
>30–40	Increased time to pregnancy Decreased number of gestational days Increased preterm birth	Sallmén et al. 1995 Jelliffe-Pawlowski et al. 2006 Jelliffe-Pawlowski et al. 2006
>40–50	Increased preterm birth	Jelliffe-Pawlowski et al. 2006

FSH = follicle-stimulating hormone; LH = luteinizing hormone

Effects in Females at Blood Pb Levels ≤10 µg/dL. As discussed above, most epidemiology studies evaluating adverse effects of Pb on female reproductive function reported mean PbB ≤10 µg/dL. Although some studies provide evidence showing associations between PbB ≤10 µg/dL and effects on serum reproductive hormones (Chang et al. 2006; Chen et al. 2016; Krieg 2007), fertility (Chang et al. 2006), spontaneous abortion (Lamadrid-Figueroa et al. 2007; Yin et al. 2008), and preterm birth (Li et al. 2017b; Rabito et al. 2014; Taylor et al. 2015; Vigeh et al. 2011), many studies show no associations between PbB and these outcomes. In general, most studies are limited by small sample sizes, although, as discussed below, some studies were of larger populations. The basis for differences in study outcomes is not readily apparent, although several factors may contribute, including low samples size, timing of evaluations in menstrual and life cycles, and inclusion of study participants identified from fertility clinics. Results are summarized in Table 2-38, with study details provided in the *Supporting Document for Epidemiological Studies for Lead* Table 12.

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Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Effects on serum hormone levels			
Chang et al. 2006	Mean: 3.55	Estradiol	β coefficient pg/mL per $\mu\text{g/dL}$ (SE): 1.18 (0.60); $p=0.049^*$
Case control study; $n=147$			
Chen et al. 2016	Median: 4.1	FSH	β coefficients (SE)
Cross-sectional study; $n=1,571$ postmenopausal women	• Q1: <2.7 ($n=558$)		• Q3: 0.047 (0.015); $p<0.01^*$
	• Q2: 2.7–4.09 ($n=572$)		• Q4: 0.046 (0.016); $p<0.01^*$
	• Q3: 4.1–5.98 ($n=585$)	LH	β coefficients (SE), Q4: 0.037 (0.016); $p<0.05^*$
	• Q4: >5.98 ($n=571$)	Estradiol	β coefficients (SE), Q4: -0.021 (0.020)
		Testosterone	β coefficients (SE), Q4: -0.016 (0.020)
		Sex hormone binding globulin	β coefficients (SE), Q4: 0.048 (0.016); $p<0.01^*$
Jackson et al. 2011	Mean: 0.87	FSH	β coefficient (IU/L per $\mu\text{g/dL}$): -2.5 (-11.2, 7.0)
Longitudinal cohort study; $n=252$		LH	β coefficient (mg/L per $\mu\text{g/dL}$): 2.5 (-12.3, 19.9)
		Estradiol	β coefficient (pg/mL per $\mu\text{g/dL}$): 4.9 (-5.0, 15.9)
		Progesterone	β coefficient (ng/mL per $\mu\text{g/dL}$): 4.6 (-12.2, 24.6)
Krieg 2007	Gmean: 2.2	FSH	• Slope pre-menopausal (IU/L per $\mu\text{g/dL}$): 8.3 (2.2); 95% CI 3.8, 12.7; $p=0.0006^*$
Cross-sectional study; $n=3,375$			• Slope post-menopausal (IU/L per $\mu\text{g/dL}$): 22.2 (4.3); 95% CI 13.5, 30.8; $p=0.0000^*$
			• Slope both ovaries removed (IU/L per $\mu\text{g/dL}$): 32.6 (11.2); 95% CI 10.1, 55.1; $p=0.0054^*$
		LH	• Slope pre-menopausal (IU/L per $\mu\text{g/dL}$): 1.7 (1.2); 95% CI -0.6, 4.1; $p=0.1486$
			• Slope post-menopausal (IU/L per $\mu\text{g/dL}$): 6.2 (1.6); 95% CI 3.0, 9.5; $p=0.0003^*$

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Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Pollack et al. 2011	Mean: 0.93	Estradiol	<ul style="list-style-type: none"> Slope both ovaries removed (IU/L per $\mu\text{g/dL}$): 10.0 (4.4); 95% CI 1.1, 18.9; p=0.0279*
Longitudinal cohort study; n=252		FSH	β coefficient (pg/mL per $\mu\text{g/dL}$): 0.03 (-0.05, 0.11)
		LH	β coefficient (mIU/mL per $\mu\text{g/dL}$): -0.01 (-0.07, 0.06)
		Progesterone	β coefficient (ng/mL per $\mu\text{g/dL}$): 0.02 (-0.06, 0.10)
			β coefficient (ng/mL per $\mu\text{g/dL}$): 0.06 (-0.04, 0.17)
Fertility			
Bloom et al. 2010	Mean: 0.82	Oocyte fertilization (<i>in vitro</i>)	RR: 1.09 (0.72, 1.65).
Longitudinal cohort study; n=15			
Bloom et al. 2011	Mean: 1.54	Achieving pregnancy over 12 menstrual cycles	β coefficient (probability of pregnancy per $\mu\text{g/dL}$): -0.031 (95% CI -1.066, 1.004); p=0.954
Longitudinal cohort study; n=80			
Chang et al. 2006	Mean:	Infertility	OR for PbB >2.5 versus ≤ 2.5 $\mu\text{g/dL}$: 2.94 (95% CI 1.18, 7.34); p=0.021*
Case control study; n=147	<ul style="list-style-type: none"> All: 3.12 Controls: 2.78 Cases: 3.55 		
Pregnancy outcome			
Bloom et al. 2015	Mean: 0.71	Duration of gestation	Regression coefficient gestational age per $\mu\text{g/dL}$ T3: 0.14 (-0.81, 1.09)
Case control study; n=235	Tertiles (mean): <ul style="list-style-type: none"> T1: not reported T2: 0.55 T3: 0.73 		

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Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL)	Outcome evaluated	Result ^c
Garcia-Esquinas et al. 2014 Birth cohort study; n=100	Gmean: 1.83	Duration of gestation	Mean difference in gestational age (weeks) per 2-fold increase in PbB: 0.02 (95% CI -0.44, 0.47)
Gundacker et al. 2010 Cross-sectional study; n=30	Median PbB: 2.5 Median Pb (placenta): 25.8 µg/kg	Spontaneous abortion	Placenta Pb concentration in women with a history of miscarriage was higher (n=8; p=0.039) than in women with no history of miscarriage (n=22)*
Lamadrid-Figueroa et al. 2007 Cross-sectional study; n=207	Mean PbB: 6.24 (4.48) Mean plasma Pb: 0.014 Mean plasma/blood Pb ratio: 0.22% (tertile values not reported)	Spontaneous abortion	IRR PbB: 0.93; p=0.56 IRR Plasma Pb: 1.12; p=0.22 Plasma/blood Pb ratio: 1.18; p=0.02* IRR for T2 plasma/blood Pb ratio: 1.161; p=0.612 IRR for T3 plasma/blood Pb ratio: 1.903; p=0.015*
Li et al. 2017b Birth cohort study; n=3,125	Mean (range): 1.5 (0.02-5.46) Stratified: • Low: <1.18 • Medium: 1.18–1.70 • High: ≥1.71	Preterm birth	• OR Medium PbB: 2.33 (1.49, 3.65); p<0.001* • OR High PbB: 3.09 (2.01, 4.76); p<0.001*
Perkins et al. 2014 Birth cohort; n=949	Estimated mean PbB: 0.4 µg/dL Mean RBC: 1.22 µg/dL Quartile RBC (µg/dL): • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02	Duration of gestation	β coefficient Q4 gestational age (weeks) per µg/dL: -0.17 (-0.51, 0.16)
Rabito et al. 2014 Birth cohort; n=98	Second trimester mean: 0.42 Third trimester mean: 0.45	Preterm birth	OR second trimester: 1.66 (1.23, 2.23); p<0.01* OR third trimester: 1.24 (1.01, 1.52); p=0.04*

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Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$)	Outcome evaluated	Result ^c
Taylor et al. 2013, 2015 Longitudinal cohort study; n=3,870	Mean: 3.67 Median: 3.42	Preterm birth	OR for PbB ≥ 5.0 : 2.0 (1.35, 3.00); p=0.001*
Vigeh et al. 2010 Longitudinal cohort study; n=351	Mean: 3.8	Spontaneous abortion	OR (log PbB): 0.331 (0.011, 10.096); p=0.53
Vigeh et al. 2011 Longitudinal cohort study; n=44 women with preterm birth; n=304 women with term birth	Mean: • Term birth: 3.72 • Preterm birth: 4.52	Preterm birth	OR: 1.41 (1.08, 1.84)*
Yin et al. 2008 Case-control study; n=80	Control (term birth): 4.5 Spontaneous abortion: 5.3	Spontaneous abortion	PbB was higher in cases of anembryonic pregnancy during gestational weeks 8–13 compared to controls with term births (p=0.03)*.
Zhu et al. 2010 Retrospective cohort; n=43,288 mother-infant pairs (n=3,519 preterm birth; n=39,769 term birth)	PbB Mean: 2.1 Quartiles: • Q1: ≤ 1.0 • Q2: 1.1–2.0 • Q3: 2.1–3.0 • Q4: 3.1–9.9	Preterm birth	Adjusted ORs did not show an increased risk of preterm birth for any quartile. Q4: 1.04 (0.89, 1.22)

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 12 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.^cAsterisk and bold indicate association with PB; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.CI = confidence interval; FSH = follicle-stimulating hormone; Gmean = geometric mean; IRR = incidence rate ratio; LH = luteinizing hormone; OR = odds ratio; Pb = lead; PbPl = Pb concentration in placenta ($\mu\text{g/kg}$); RBC = red blood cell; RR = relative risk; SE = standard error

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Serum hormone levels and estrus cycle. Results of epidemiological studies on associations between PbB ≤ 10 $\mu\text{g/dL}$ and serum hormone levels show conflicting results (Table 2-38). The strongest evidence showing that chronic Pb exposure alters serum hormone levels is from a large cross-sectional study (mean PbB: 2.2 $\mu\text{g/dL}$) participating in the NHANES III study (Krieg 2007). Serum levels of FSH (IU/L) increased with PbB in both pre-menopausal and post-menopausal women. Serum levels of LH increased with PbB in post-menopausal women, but not pre-menopausal women. The lowest PbBs associated with a significant increase in FSH in pre- and post-menopausal women were 4.1 $\mu\text{g/dL}$ and 2.4 $\mu\text{g/dL}$, respectively. The lowest PbB associated with a significant increase in FSH in post-menopausal women was 2.8 $\mu\text{g/dL}$ (slope \pm SE 8.6 \pm 3.3; 95% CI 2.1, 15.2; $p=0.0109$). Increases in serum FSH and LH were also observed in women who had total ovariectomy, indicating that increased hormone levels may be related to effects on the hypothalamus or pituitary (Krieg 2007). A large cross-sectional study of postmenopausal Chinese women also found that elevated serum hormones levels were positively associated with PbB. Increased FSH was observed in the two highest PbB quartiles (4.1–5.9 and >5.9 $\mu\text{g/dL}$), with LH increased in the highest quartile (Chen et al. 2016). SHBG was also increased in the highest quartile. No associations were observed between Pb and serum levels of FSH, LH, estradiol, or progesterone or menstrual cycle length in a smaller study of pre-menopausal women with a mean PbB of 0.87 $\mu\text{g/dL}$ (Jackson et al. 2011). In this same study population, when PbB was examined by tertiles, increased serum progesterone levels were observed in the second PbB tertile (0.73–1.10 $\mu\text{g/dL}$) compared to the lowest tertile (0.30–0.72 $\mu\text{g/dL}$), but no effects were observed in the highest PbB tertile (1.11–6.20 $\mu\text{g/dL}$) compared to the lowest (Pollack et al. 2011). In this study population, no association was observed between PbB and anovulation. In a case-control study of women attending a fertility clinic, a significant association was observed between PbB and serum estradiol concentrations (Chang et al. 2006).

Fertility. Little epidemiological information is available on the effects of PbB ≤ 10 $\mu\text{g/dL}$ on female fertility. A prospective cohort study with a mean Pb of 1.5 $\mu\text{g/dL}$ showed no effect on achieving pregnancy over 12 menstrual cycles (Bloom et al. 2011). A case-control study of women from a fertility clinic showed a 2.9-fold risk of infertility for PbB >2.5 $\mu\text{g/dL}$ compared to PbB ≤ 2.5 $\mu\text{g/dL}$ (Chang et al. 2006). In a study of women undergoing *in vitro* fertilization, no association was observed between PbB and oocyte fertilization; however, only 15 women were included in this study. Available epidemiological studies on the effects of PbB ≤ 10 $\mu\text{g/dL}$ on fertility are limited due to small numbers of participants and study populations of women undergoing fertility treatment; thus, data are not sufficient to determine if fertility in women is affected at PbB ≤ 10 $\mu\text{g/dL}$.

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Spontaneous abortion. Few epidemiological studies have evaluated associations between PbB ≤ 10 $\mu\text{g/dL}$ and spontaneous abortion (Table 2-38). Although studies provide some evidence suggesting associations between PbB ≤ 10 $\mu\text{g/dL}$ or plasma/blood Pb ratio and spontaneous abortion, results are inconsistent. In a case-control study, PbB was significantly higher in cases of spontaneous abortion (PbB 5.3 $\mu\text{g/dL}$; $p=0.03$) during weeks 8–13, compared to women with term birth (PbB 4.5 $\mu\text{g/dL}$) (Yin et al. 2008). A cross-sectional study reported that the risk of miscarriage per 1 SD increase of plasma/blood Pb ratio [mean plasma/blood Pb ratio \pm SD (%): 0.22 \pm 0.14] was associated with an 18% greater incidence of spontaneous abortion, although the association between risk of spontaneous abortion and PbB (mean 6.24) was not significant (Lamadrid-Figueroa et al. 2007). In contrast, results of a longitudinal cohort study showed no association between PbB and spontaneous abortion during gestational weeks 13–19 (Vigeh et al. 2010).

Preterm birth. Several studies have evaluated associations between PbB ≤ 10 $\mu\text{g/dL}$ and preterm birth (<37 weeks of gestation), including three studies of larger study populations ($n=705$ – $3,870$) (Li et al. 2017b; Perkins et al. 2014; Taylor et al. 2015). Results of these studies are mixed (Table 2-38). The strongest evidence showing that chronic Pb exposure is associated with preterm birth is from two large, cohort studies (Li et al. 2017b; Taylor et al. 2013, 2015). Taylor et al. (2013, 2015) reported that when stratified into groups of PbB <5 and ≥ 5.0 $\mu\text{g/dL}$, there was a 2-fold increase in the risk of preterm birth for PbB ≥ 5.0 $\mu\text{g/dL}$ compared to PbB <5 $\mu\text{g/dL}$. In the PbB ≥ 5.0 $\mu\text{g/dL}$ group, the maximum PbB was 19.14 $\mu\text{g/dL}$, although very few PbBs were >10 $\mu\text{g/dL}$; however, the group mean PbB was not reported. In a large cohort study, the risk of preterm birth was increased in women with PbBs of 1.18–1.70 and 1.71–5.46 $\mu\text{g/dL}$, relative to women with PbBs of 0.02–1.18 $\mu\text{g/dL}$ (Li et al. 2017b). The risk of preterm birth also was increased in a longitudinal cohort study (Vigeh et al. 2011). Mean PbB in women with preterm birth was significantly higher than in women with term birth (preterm PbB: 4.52 $\mu\text{g/dL}$; term birth PbB: 3.72 $\mu\text{g/dL}$). A cohort study showed increased odds of preterm birth associated with PbB measured in the 2nd (mean: 0.42 $\mu\text{g/dL}$) and 3rd (mean: 0.45 $\mu\text{g/dL}$) trimesters (Rabito et al. 2014). ORs for risks of preterm birth were 1.66 ($p<0.01$) and 1.24 ($p=0.04$) for 2nd and 3rd trimester PbB, respectively. Other studies reported no associations between PbB and preterm birth at mean PbB of 0.71–5.70 $\mu\text{g/dL}$ (Bloom et al. 2015; Perkins et al. 2014; Zhu et al. 2010), including a large retrospective cohort study (Zhu et al. 2010) and a large case-control study (Perkins et al. 2014).

Age at menopause. A few studies had evaluated associations between Pb exposure and age at menopause (Eum et al. 2014; Popovic et al. 2005). Eum et al. (2014) found an inverse association between tibia Pb and age at onset of natural menopause (e.g., non-surgical) in a population of 434 participants in the

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Nurses Health Study cohort. In the highest tibia Pb tertile, the age at onset of menopause was 1.21 years earlier than controls. However, no associations were observed between PbB (mean PbB: <5 $\mu\text{g/dL}$) or patella Pb. In a study of 108 former smelters (mean PbB: 2.73 $\mu\text{g/dL}$), the age at onset of combined natural and surgical menopause was earlier by 7 years ($p=0.001$) compared to controls ($n=99$; PbB: 1.25 $\mu\text{g/dL}$) (Popovic et al. 2005). No difference was observed between the age at onset and natural menopause between the exposed and control groups.

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to male and female reproductive systems. Oxidative stress through ROS is a plausible mechanism for reproductive effects, as is the disruption of calcium homeostasis. Mechanisms for alterations in circulating hormone levels have been not been established. However, EPA (2014c) and NRC (2012) noted several possible mechanisms that may be involved in alterations of serum hormones, including direct inhibition of LH secretion; reduced expression of steroidogenic acute regulatory protein (a protein required in maintaining gonadotropin-stimulated steroidogenesis); altered release of pituitary hormones due to interference with cation-dependent second messenger systems; and altered binding of hormones to receptors. Pb is distributed to, and has been measured in, semen, spermatozoa, the fetus, umbilical cord blood, placenta, and follicular fluid (see Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct effects to reproductive tissues.

2.18 DEVELOPMENTAL

This section discusses developmental effects of Pb other than neurodevelopmental defects. Neurodevelopmental effects are discussed in Section 2.16 (Neurological Effects). The term “developmental” used in the discussion that follows refers to effects other than neurodevelopmental.

Overview. Numerous epidemiological studies have evaluated developmental effects (birth outcomes, birth defect, neural tube defects, decreased anthropometric measures in children, and delayed puberty) associated with Pb exposure, with the database for developmental effects dominated by environmental exposure studies with PbB ≤ 10 $\mu\text{g/dL}$. In general, studies provide mixed evidence for effects on birth outcomes (e.g., infant size) and anthropometric measures in children, but more consistent evidence for delayed puberty. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent, and several studies, including prospective studies, with PbB ≤ 10 $\mu\text{g/dL}$ show no associations with developmental outcomes.

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The following developmental effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Effects on birth outcomes (decreased birth weight, head circumference, and crown-heel length); results are mixed when compared across studies.
 - Decreased anthropometric measures in children (weight, height, head circumference, trunk length, leg length, arm length, BMI); results are mixed when compared across studies.
 - Delayed puberty in females (breast development, pubic hair development, onset of menarche); corroborated in multiple studies.
 - Delayed puberty in males (testicular volume, genitalia development, pubic hair development); a few studies with equivocal results.
- > 10 $\mu\text{g/dL}$ (based on few studies):
 - Effects on birth outcomes (low birth weight).
 - Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference).
 - Delayed puberty in females (breast development).
 - Delayed puberty in males (decreased testicular size, delayed pubic hair development, delayed penile development).

Measures of Exposure. Most studies evaluating developmental effects used maternal PbB and/or cord, infant, or child PbB as the biomarker for exposure. In some studies, Pb concentrations in red blood cells (Perkins et al. 2014), maternal bone (Afeiche et al. 2011; Cantonwine et al. 2010; Hernandez-Avila et al. 2002; Kordas et al. 2009), or hair (Sanín et al. 2001; Sanna and Vallascas 2011) were used as biomarkers.

Confounding Factors and Effect Modifiers. Numerous complicating factors may add uncertainty in the interpretation of studies examining associations between PbB and developmental effects. These factors include nutrition during pregnancy, prenatal care, adequate nutrition during infancy and childhood, SES, intercurrent diseases, alcohol consumption, smoking status, and potential exposure to other chemicals. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. As noted above, most epidemiological studies evaluated developmental effects at PbB ≤ 10 $\mu\text{g/dL}$, with few studies of PbB > 10 $\mu\text{g/dL}$. Studies of PbB ≤ 10 $\mu\text{g/dL}$ are discussed

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in detail in the section below. General trends for studies showing a relationship between PbB ≤ 10 –50 $\mu\text{g/dL}$ and developmental effects are shown in Table 2-39. Effects on birth outcomes, including decreased birth weight, head circumference, and crown-heel length have been observed at maternal PbBs of ≤ 10 –50 $\mu\text{g/dL}$. Decreased anthropometric measures in infants and children, including decreased weight, height, head circumference, trunk length, leg length, arm length, and BMI, have been observed over the PbB range of ≤ 10 –30 $\mu\text{g/dL}$. Delayed onset of puberty in males and females was observed over the PbB range of ≤ 10 –30 $\mu\text{g/dL}$. Very little data are available regarding *in utero* exposure to Pb and birth defects. Two studies that examined neural tube defects did not find associations with Pb exposure at mean blood levels over for PbB means ranging from 2.4 to 24 $\mu\text{g/dL}$ (Brender et al. 2006; Zeyrek et al. 2009). As discussed below, although epidemiological studies demonstrate developmental effects of Pb, results across studies are inconsistent, with several studies reporting no association between PbB and developmental effects. For example, results of effects on birth outcomes in study populations with maternal PbB ≤ 10 $\mu\text{g/dL}$ are equivocal (see Tables 2-40 and 2-41). For studies with maternal PbB > 10 $\mu\text{g/dL}$, equivocal results also were observed for associations between PbB and birth weight and length (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤ 10 $\mu\text{g/dL}$) in most studies.

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) ($\mu\text{g/dL}$)	Effects associated with Pb exposure	References
≤ 10	Effects on birth outcome (decreased birth weight, crown-heel length, head circumference)	Bornschein et al. 1989; González - Cossío et al. 1997; Nishioka et al. 2014; Odland et al. 1999; Taylor et al. 2013, 2015; Wang et al. 2017b, 2017b; Xie et al. 2013; Zhu et al. 2010
	Minor congenital anomalies	Needleman et al. 1984
	Decreased anthropometric measures in children (decreased weight, height, head circumference, waist circumference, trunk length, leg length, arm length, body mass index, body fat)	Afeiche et al. 2011; Alvarez-Ortega et al. 2019; Dallaire et al. 2014; Deierlein et al. 2019; Hauser et al. 2008; Hong et al. 2014; Ignasiak et al. 2006; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Raihan et al. 2018; Schell et al. 2009; Yang et al. 2013a
	Delayed puberty in females (breast development, pubic hair development, onset of menarche)	Denham et al. 2005; Den Hond et al. 2011; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b

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Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Delayed puberty in males (testicular volume, genitalia development, pubic hair development)	Hauser et al. 2008; Williams et al. 2010, 2019
>10–30	Effects on birth outcome (decreased birth weight)	Chen et al. 2006; Hernandez-Avila et al. 2002
	Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference)	Frisancho and Ryan 1991; Kerr et al. 2019; Tomoum et al. 2010
	Delayed puberty in females (breast development)	Liu et al. 2019b; Tomoum et al. 2010
	Delayed puberty in males (decreased testicular size, delayed pubic hair development; delayed penile development)	Tomoum et al. 2010
>30–50	Effects on birth outcome (low birth weight)	Jelliffe-Pawlowski et al. 2006

Table 2-40. Effects on Birth Outcomes at Blood Lead Concentration (PbB) ≤10 µg/dL

Reference (population size)	Birth outcome			
	Birth weight	Height or C-H length	SGA	Head circumference
Al-Saleh et al. 2014 (n=1,577)	0 ^a	0	0	0
Bloom et al. 2015 (n=235)	0 ^a	0	–	0
Bornschein et al. 1989 (n=202)	↓ ^a	↓	–	0
Garcia-Esquinas et al. 2014 (n=97)	0 ^a	0	–	–
González-Cossío et al. 1997 (n=272)	0 ^b	–	–	–
Kim et al. 2017b (n=280)	0 ^b	↑ (M), 0 (F)	–	0
Nishioka et al. 2014 (n=386)	↓ ^b	–	–	–
Odland et al. 1999 (n=50)	↓ ^{a,b}	–	–	–
Perkins et al. 2014 (n=949)	0 ^{a,b}	0	–	0
Rabito et al. 2014 (n=98)	0 ^a	–	–	–
Rodosthenous et al. 2017 (n=946)	–	–	0	–
Taylor et al. 2015 (n=4,285)	↓ ^b	↓	–	↓
Thomas et al. 2015 (n=1,835)	–	–	0	–
Wang et al. 2017b	↓	0	↓	0
Wang et al. 2017c	↑ (M), 0 (F)	0 (F)	–	0

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Table 2-40. Effects on Birth Outcomes at Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$

Reference (population size)	Birth outcome			
	Birth weight	Height or C-H length	SGA	Head circumference
Xie et al. 2013 (n=252)	↓ ^b	0	–	0
Zhu et al. 2010 (n=43,288)	↓ ^b	–	0	–

^aBirth weight not adjusted for gestational age^bBirth weight adjusted for gestational age

↓ = decrease in outcome measure; ↑ = increase in outcome measure; 0 = no effect on outcome measure; – = not assessed; C-H = crown-heel; F = female; M = male; SGA = small for gestational age

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}^a$

Reference and study population ^b	PbB ($\mu\text{g/dL}$) ^c	Outcome evaluated	Result ^d
Al-Saleh et al. 2014	Maternal PbB mean: 2.897	Birth weight	OR: 1.107 (0.797, 1.538); p=0.545
Cross-sectional study; n=1578 mother-infant pairs		Birth height	OR: 1.299 (0.945, 1.786); p=0.107
		Crown-heel length	OR: 1.061 (0.795, 1.415); p=0.689
		SGA	OR: 1.168 (0.837, 1.631); p=0.362
		Head circumference	OR: 1.007 (0.724, 1.400); p=0.968
Bloom et al. 2015	Maternal PbB mean: 0.71 Teriles:	Apgar	OR: 1.027 (0.787, 1.341); p=0.842
		Birth weight	Linear regression coefficient (g per $\mu\text{g/dL}$) T3: -34.85 (-97.76, 128.06); p-trend=0.202
		Birth length	Linear regression coefficient (cm per $\mu\text{g/dL}$) T3: 0.14 (-0.81, 1.09); p-trend:0.671
		Head circumference	Linear regression coefficient (cm per $\mu\text{g/dL}$) T3: -0.33 (-1.07, 0.41); p-trend: 0.132
Bornschein et al. 1989	PbB:	Birth weight	Regression coefficient (g per ln $\mu\text{g/dL}$) for all births: -114; p<0.001*.
Prospective study; n=202 mother-infant pairs	Mean (SD): 7.5		Regression coefficient (g per ln $\mu\text{g/dL}$) with significant interaction with maternal age (p=0.0073)*:
			maternal age 18 years: -58*
			maternal age 30 years: -601*
		Birth length	Regression coefficient (cm per ln $\mu\text{g/dL}$): -2.5; p=0.019*
		Head circumference	Regression coefficient (cm per ln PbB $\mu\text{g/dL}$): 0.0 p=0.97

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB (µg/dL) ^c	Outcome evaluated	Result ^d
García-Esquinas et al. 2014 Birth cohort study; n=100 mother-infant pairs	Maternal PbB Gmean: 1.83	Birth weight	Adjusted mean difference in grams for a 2-fold increase in PbB (µg/L): 62.4 (-73.1, 197.8)
		Birth length	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.17 (-0.56, 0.91)
		Abdominal diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/d): 0.31 (-0.52, 1.15)
		Cephalic diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.15 (-0.21, 0.51)
		Birth weight	Regression coefficient: <ul style="list-style-type: none">• Maternal PbB for Q4: -98.30 (59.55); p=0.100• Umbilical cord PbB for Q4: -41.74 (64.04); p=0.514
González-Cossío et al. 1997 Birth cohort study; n=272 mother-infant pairs	PbB: <ul style="list-style-type: none">• Maternal<ul style="list-style-type: none">◦ Mean (SD): 8.9 (4.1)◦ Quartiles:<ul style="list-style-type: none">▪ Q1: ≤5.8▪ Q2: 5.9–8.0▪ Q3: 8.1–11.0▪ Q4: ≥11.1• Umbilical cord<ul style="list-style-type: none">◦ Mean (SD): 7.1 (3.5)◦ Quartiles<ul style="list-style-type: none">▪ Q1: ≤4.6▪ Q2: 4.7–6.1▪ Q3: 6.2–8.5▪ Q4: ≥8.6	Birth weight	

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Kim et al. 2017b Prospective longitudinal study; n=280 mother-infant pairs	PbB: Umbilical cord, mean (SE) • All: 1.31 (0.06) • Boys: 1.39 (0.09) • Girls: 1.21 (0.07)	Birth weight	Regression coefficient: • Boys: 0.010 (-0.014, 0.034); p=0.403 • Girls: 0.001 (-0.025, 0.027); p=0.950
		Birth length	Regression coefficient: • Boys: 0.017 (0.003, 0.031); p=0.019* • Girls: 0.007 (-0.010, 0.025); p=0.410
		Head circumference	Regression coefficient: • Boys: 0.010 (-0.001, 0.022); p=0.083 • Girls: -0.007 (-0.016, 0.002); p=0.148
		Ponderal index	Regression coefficient: • Boys: -0.055 (-0.103, -0.006); p=0.027* • Girls: -0.009 (-0.062, 0.045); p=0.748
Nishioka et al. 2014 Cohort study; n=386 mother-infant pairs	Maternal PbB mean at gestational weeks: • 12 weeks: 0.98 • 25 weeks: 0.92 • 36 weeks: 0.99	Birth weight	Regression coefficient based on log $\mu\text{g}/\text{dL}$: • Infant males: -0.151 (p<0.05)* • Infant females: -0.098 (p>0.05)
Odland et al. 1999 Cohort study; n=262 mother-infant pairs	Maternal, mean (range); p-values compare Russian and Norwegian cohorts • Russian cohort: 2.9 (0.83–13.5) • Norwegian cohort: 2.3 (0.41–3.9); p<0.001	Birth weight	Regression coefficient, combined Russian and Norwegian cohorts [g per $\mu\text{mol}/\text{L}$ (g per 20.7 $\mu\text{g}/\text{dL}$): -1,068 (95% CI -2,134, -2); p<0.05*

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Perkins et al. 2014 Birth cohort study; n=829 mother-infant pairs	Maternal RBC Pb concentration ($\mu\text{g}/\text{dL}$) mean: 1.22 Quartiles for RBC Pb; mean: • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02 Estimated maternal PbB mean: 0.4	Birth weight Birth length Head circumference	Linear regression β coefficient for RBC ($\mu\text{g}/\text{dL}$) Q4: -47 (-128, 35); p-trend: 0.27 Linear regression β coefficient for RBC ($\mu\text{g}/\text{dL}$) Q4: -0.15 (-0.54, 0.23); p-trend: 0.37 Linear regression β coefficient for RBC ($\mu\text{g}/\text{dL}$) Q4: -0.08 (-0.33, 0.16); p-trend: 0.56
Rabito et al. 2014 Birth cohort study; n=98 mother-infant pairs	Maternal 2 nd trimester PbB mean: 0.42 Maternal 3 rd trimester PbB mean: 0.45	Birth weight	Linear regression β coefficient, g per $\mu\text{g}/\text{dL}$ maternal: • 2 nd trimester: -43.21 (-88.6, 2.18); p=0.06 • 3 rd trimester: β not reported; p=0.68 • Delivery: β not reported; p=0.83
Rodosthenous et al. 2017 Prospective cohort study; n=944 mother-infant pairs	Maternal 2 nd trimester PbB: 3.7 • Quartiles: o Q1: <1.93 o Q2: 1.93–2.79 o Q3: 2.80–4.53 o Q4: >4.53	Birthweight-for-gestational age z-score SGA	Linear regression β for a doubling for PbB: -0.06 (-0.13, 0.003); p=0.06 Logistic regression OR Q4: 1.62 (0.99–2.65)
Taylor et al. 2013, 2015 Longitudinal cohort study; n=4,285 mother-infant pairs	Maternal PbB mean: 3.67 Population stratified by PbB <5.0 and ≥ 5.0	Birth weight Head circumference Crown-heel length	β coefficient (g per $\mu\text{g}/\text{dL}$): -13.23 (-23.75, -2.70); p=0.014* β coefficient (cm per $\mu\text{g}/\text{dL}$): -0.04 (-0.07, -0.06) ^e ; p=0.021* β coefficient (cm per $\mu\text{g}/\text{dL}$): -0.05 (-0.10, -0.00); p=0.034*

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Thomas et al. 2015 Prospective cohort; n=1,835 mother-infant pairs	Maternal PbB median: 0.59 Teriles: • T1: <0.52 • T2: 0.52–1.04 • T3: >1.04–4.04	SGA	Adjusted RR for T3 (95% CI): 1.19 (0.65, 2.18)
Wang et al. 2017b Prospective cohort study; n=3,125 mother-infant pairs	Maternal serum Pb mean: 1.50 Teriles: • T1: <1.18 • T2: 1.18–1.70 • T3: ≥ 1.71	Birth weight Birth length Head circumference Chest circumference	Regression coefficient β: -2.74 (-5.17, -0.31); p=0.03* Regression coefficient β : -0.013 (-0.026, 0.001); p=0.06 Regression coefficient β : -0.008 (-0.019, 0.004); p=0.18 Regression coefficient β : -0.008 (-0.018, 0.002); p=0.13
Wang et al. 2017c Cross-sectional study; n=1,009 mother-infant pairs	PbB: Cord PbB, Gmean (95% CI) All: 4.07 (3.98, 4.17) Infant boys: 4.07 (3.89, 4.17) Infant girls: 4.17 (3.98, 4.36)	SGA Birth weight	 • OR T2: 1.45 (1.04, 2.02); p=0.03* • OR T3: 1.69 (1.22, 2.34); p=0.002* Regression coefficient β (95%), per 1-unit increase in log ₁₀ -transformed PbB: • All: 60.78 (-66.30, 187.85); p=0.35 • Boys: 182.32 (15.24, 349.39); p=0.03* • Girls: -96.06 (-289.23, 97.10); p=0.33
		Birth length	Regression coefficient β (95%), per 1-unit increase in log ₁₀ -transformed PbB: • All: 0.32 (-0.18, 0.82); p=0.21 • Boys: not reported • Girls: 0.30 (-0.46, 1.05); p=0.44

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$) ^c	Outcome evaluated	Result ^d
Xie et al. 2013 Birth cohort study; n=252 mother-infant pairs	Maternal PbB mean: 3.53	Head circumference	Regression coefficient β (95%), per 1-unit increase in log ₁₀ -transformed PbB: <ul style="list-style-type: none"> All: -0.36 (-0.78, 0.06); p=0.09 Boys: -0.50 (-1.09, 0.09); p=0.10 Girls: -0.32 (-0.91, 0.27); p=0.29
		Ponderal index	Regression coefficient β (95%), per 1-unit increase in log ₁₀ -transformed PbB: <ul style="list-style-type: none"> All: -0.01(-0.10, 0.09); p=0.94 Boys: 0.10 (-0.03, 0.23); p=0.12 Girls: -0.17 (-0.31, -0.02); p=0.02*
		Birth weight	β coefficient (g per square root $\mu\text{g/dL}$): -148.99 (-286.33, -11.66); p=0.03*
		Birth length	β coefficient (cm per square root $\mu\text{g/dL}$): -0.46 (-1.25, 0.34); p=0.26
		Head circumference	β coefficients (cm per square root $\mu\text{g/dL}$): -0.37 (-0.78, 0.19); p=0.24

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Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL) ^c	Outcome evaluated	Result ^d
Zhu et al. 2010	Maternal PbB mean: 2.1	Birth weight	β coefficient g per µg/dL (95% CI): 0: reference 1: -27.4 (-17.1, -37.8)* 2: -38.8 (-24.1, -53.4)* 3: -47.5 (-29.6, -65.4)* 4: -54.8 (-34.2, -75.5)* 5: -61.3 (-38.2, -84.4)* 6: -67.2 (-41.8, -92.5)* 7: -72.5 (-45.2, -99.9)* 8: -77.6 (-48.3, -106.8)* 9: -82.3 (-51.2, -113.3)* 10: -86.7 (-54.0, -119.4)*
Retrospective cohort study; n=43,288 mother-infant pairs			SGA
			Adjusted OR for Q4: 1.07 (0.93, 1.23)

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 13 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.^cValues are for maternal PbB, unless otherwise specified.^dAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.^eValues are reported; the value for the β coefficient is outside of the 95% CI.

CI = confidence interval; Gmean = geometric mean; OR = odds ratio; Pb = lead; RBC = red blood cell; RR = relative risk; SD = standard deviation; SE = standard error; SGA = small for gestational age

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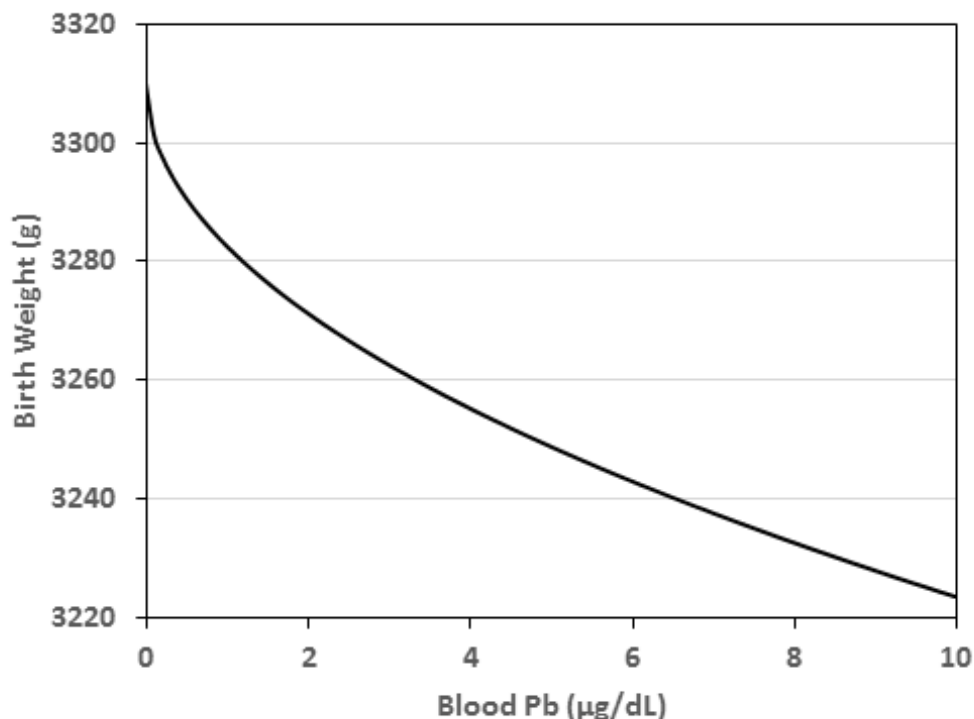
Effect at Blood Pb Levels $\leq 10 \mu\text{g/dL}$. Epidemiology studies have reported developmental effects, including birth outcomes, birth defects, anthropometric measures in children, and delayed onset of puberty, at mean PbB $\leq 10 \mu\text{g/dL}$. Study details are provided in *Supporting Document for Epidemiological Studies for Lead*, Table 13. Results of studies on associations between PbB and adverse effects on birth outcomes and anthropometric measures are mixed when compared across studies. Delayed onset of puberty in females has been corroborated in several studies. Fewer studies are available regarding effects of Pb on onset of puberty in males, with equivocal results. Exposure to Pb has not been shown to cause birth defects in humans. Neural tube defects have not been associated with Pb exposure and findings of a single study showing minor anomalies have not been corroborated.

Birth outcomes. An overview of results of studies that evaluated associations between Pb exposure and birth outcomes (infant weight, height or crown-heel length, small for gestation age [SGA], head circumference, and ponderal index) at maternal PbB $\leq 10 \mu\text{g/dL}$ is shown in Table 2-40, with more detailed results in Table 2-41. Studies include two prospective studies (Bornschein et al. 1989; Thomas et al. 2015), several studies of large populations ($n=829\text{--}43,288$) (Al-Saleh et al. 2014; Perkins et al. 2014; Rodosthenouse et al. 2017; Taylor et al. 2015; Thomas et al. 2015; Wang et al. 2017b, 2017b; Zhu et al. 2010), and cohort and case-control studies of smaller ($n=98\text{--}386$) populations (Bloom et al. 2015; Garcia-Esquinas et al. 2014; González-Cossío et al. 1997; Kim et al. 2017b; Nishioka et al. 2014; Rabito et al. 2014). As shown in Table 2-41, results of most studies show either decreases or no change in birth outcomes. Some positive associations between PbB and birth outcomes have been reported. A large cross-sectional study ($n=1,009$) reported a positive association between umbilical cord PbB (mean: $4.07 \mu\text{g/dL}$) and birth weight in male infants, but no change for female infants (PbB mean: $4.17 \mu\text{g/dL}$) (Wang et al. 2017c). A longitudinal study showed a positive association between umbilical cord PbB in infant boys (mean: $1.39 \mu\text{g/dL}$) and birth length, but an inverse association for ponderal index (calculated relationship between body mass and height); no associations were observed for infant girls (PbB mean: $1.21 \mu\text{g/dL}$) (Kim et al. 2017b). In a small ($n=202$) prospective study, Bornschein et al. (1989) reported associations between maternal PbB (mean $7.5 \mu\text{g/dL}$) and decreased birth weight and length. The size of the effect of PbB varied with maternal age ($p<0.007$), with a 58 g per lnPbB decrease for pregnancies at age 18 years and a 601 g decrease per ln PbB ($\mu\text{g/dL}$) for pregnancies at age 30 years. In the complete birth cohort from this study, which included mothers who declined participation in the infant follow-up ($n=861$), the decline in birth weight was -114 g per ln PbB. Results of the largest cohort study, a retrospective study of $>43,000$ participants (mean PbB: $2.1 \mu\text{g/dL}$), showed an inverse association between PbB and birth weight (Zhu et al. 2010). The best fitting model was a linear change in birth weight with square root of PbB (Figure 2-7). The model predicts a 34 g decrease in birth weight for an

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increase in PbB from 1 to 5 $\mu\text{g/dL}$ and a 59 g decrease for an increase in PbB from 1 to 10 $\mu\text{g/dL}$ (adjusted for confounders).

Figure 2-7. Relationship Between Blood Lead Concentration (PbB) and Birth Weight at PbB ≤ 10 $\mu\text{g/dL}$



Source: Zhu et al. 2010

Results of a longitudinal cohort study of 4,285 mother-infant pairs (maternal PbB mean: 2.1 $\mu\text{g/dL}$; range 0.42–19.14) showed inverse associations between birth weight, crown-heel length, and head circumference for participants with PbB ≥ 5 $\mu\text{g/dL}$ compared to PbB < 5 $\mu\text{g/dL}$ (Taylor et al. 2015). A prospective cohort study of 3,125 mother infant pairs observed an inverse association between maternal serum Pb (mean: 1.50 $\mu\text{g/dL}$) and birth weight and SGA (Wang et al. 2017b). Other smaller cohort studies also showed associations between maternal PbB ≤ 10 $\mu\text{g/dL}$ and decreased birth weight (Nisioka et al. 2014; Odland et al. 1999). In contrast, other studies, including a prospective study and cohort studies of large populations, did not find associations between PbB and birth outcome measures. A prospective study of 1,835 mother-infant pairs did not find an association between PbB and SGA, with PbB data stratified by tertiles (range for highest tertile: 1.04–4.04 $\mu\text{g/dL}$) (Thomas et al. 2015). Similarly, no associations between maternal PbB and decreased birth weight, length, or head circumference were

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observed in a cohort study of 829 participants (estimated PbB mean of 0.4 µg/dL) (Perkins et al. 2014), or in a cross-sectional study of 1,578 participants (Al-Saleh et al. 2014). Smaller cohort studies also report no associations between PbB and adverse birth outcome measures (Bloom et al. 2015; Garcia-Esquinas et al. 2014; González-Cossío et al. 1997; Rabito et al. 2014). Equivocal findings for birth outcomes in studies examining effects at maternal PbB ≤10 µg/dL are not surprising, given that prospective studies at maternal PbB >10 µg/dL also have reported conflicting results for adverse effects on birth outcomes (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). For example, two prospective studies found no associations between PbB and birth weight in birth cohorts that had mean maternal PbBs >10 µg/dL (Factor-Litvak et al. 1991; McMichael et al. 1986).

Birth defects. Few studies have evaluated associations between *in utero* exposure to Pb and birth defects. Details of studies evaluating PbB ≤10 µg/dL are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 13. No association was observed between PbB and neural tube defects in a case-control study (n=409) with mean maternal PbB of 2.5 µg/dL (Brender et al. 2006). Other epidemiological studies that have reported associations between Pb in exposure media (e.g., water, soil) and neural tube defects are limited by the lack of PbB measurement (Bound et al. 1997; Huang et al. 2011; Irgens et al. 1998). An early cross-sectional study of birth outcomes examined associations between PbB and congenital anomalies using hospital records on 5,183 deliveries in Boston, Massachusetts (Needleman et al. 1984). The RR of an anomaly increased with increasing cord PbB; the RR (relative to PbB 0.7 µg/dL) was 1.87 (95% CI 1.44, 2.42) for PbB of 6.3 µg/dL and increased to 2.39 (95% CI 1.66, 3.43) at 15 µg/dL and 2.73 (95% CI 1.80, 4.16) at 24 µg/dL. The anomalies were considered to be minor (hemangiomas, lymphangiomas, hydrocele, minor skin anomalies, undescended testicle) and no specific anomaly was associated with PbB. Limitations of this study are that it was a cross-sectional study of a convenience sample with outcomes obtained from hospital records. Associations between PbB and congenital anomalies have not been corroborated. A case-control study of 97 cases and 201 controls did not find an increased risk for congenital heart defects (Liu et al. 2018a). For the highest umbilical cord PbB tertile (≥0.826 µg/dL), the OR (95% CI) for congenital heart defects was 1.67 (0.88, 3.17).

Anthropometric measures in children. An overview of results of studies evaluating associations between Pb exposure and growth of infants and children (aged 0.5–15 years) at maternal and/or offspring PbB ≤10 µg/dL is shown in Table 2-42, with more detailed results in Table 2-43. Studies include five prospective studies (Dallaire et al. 2014; Deierlein et al. 2019; Lamb et al. 2008 Kim et al. 2017b; Renzetti et al. 2017), cross-sectional studies of large (n=899–1,050) populations (Afeiche et al. 2011;

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Hong et al. 2014; Ignasiak et al. 2006), and several smaller (n=108–729) cohort and cross-sectional studies (Alvarez-Ortega et al. 2019; Hauser et al. 2008; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Raihan et al. 2018; Schell et al. 2009; Yang et al. 2013a). Most studies report inverse associations between Pb exposure and height, with mixed results for weight and BMI (Table 2-42). In a prospective longitudinal study of girls (n=692; mean PbB: 1.16 µg/dL), height, BMI, waist circumference, and percent body fat were decreased in participants with PbB ≥1 µg/dL, compared to participants with PbB <1 µg/dL; decreases were observed at yearly assessments at ages 7–14 years (Deierlein et al. 2019). The Renzetti et al. (2017) prospective study (n=513 mothers) reported inverse associations between 3rd pregnancy trimester maternal PbB (mean: 3.1 µg/dL) and weight-for-age and height-for-age, but no associations for BMI or percentage body fat. No associations were observed between 2nd trimester PbB or cord PbB. In contrast, a prospective study of 280 children (18–27 months) observed positive associations between umbilical cord PbB (mean: 1.31 µg/dL) and weight and BMI, but not height; no associations were observed at 18 or 27 months (Kim et al. 2017b). A small (n=290) prospective study showed an association between cord PbB (mean 4.8 µg/dL) and small decreases in height and head circumference, but not for weight or BMI (Dallaire et al. 2014). Similarly, Lamb et al. (2008) did not find an association between maternal PbB and height or BMI at maternal PbB means of 5.60–20.56 µg/dL (means for different geographic locations). In contrast, results of large case-control studies showed inverse associations between maternal bone Pb and weight (Afeiche et al. 2011), maternal PbB and weight and height (Hong et al. 2014), and child PbB and several growth measures, including weight, height, and BMI (Ignasiak et al. 2006). The largest inverse association for decreased weight was observed for maternal bone Pb in females assessed at 2–5 years of age; the mean PbB in children was 3.8 µg/dL (Afeiche et al. 2011). At the 5-year assessment, body weight in females was decreased by approximately 172 g for each 1-SD increase in maternal bone Pb. Smaller case-control and cohort studies reported consistent inverse associations between PbB and height, with equivocal findings for weight, and no associations for BMI.

Table 2-42. Overview of Decreased Anthropometric Measures in Children at Blood Lead Concentration (PbB) ≤10 µg/dL

Reference	Age at time of assessment (years)	Anthropometric measurements		
		Weight	Height	BMI
Afeiche et al. 2011	1–5	↓ (F); 0 (M)	–	–
Alvarez-Ortega et al. 2019	5–16	↓ (F); 0 (M)	↓ (F); 0 (M)	↓ (F); 0 (M)
	5–11	0	0	0
	12–16	↓	↓	↓
Dallaire et al. 2014	8–14	0	↓	0
Deierlein et al. 2019	7–14	↓	↓	↓

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Table 2-42. Overview of Decreased Anthropometric Measures in Children at Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$

Reference	Age at time of assessment (years)	Anthropometric measurements		
		Weight	Height	BMI
Hauser et al. 2008	8–9	0	↓	0
Hong et al. 2014	0.5–2	↓	↓	–
Ignasiak et al. 2006	7–15	↓ (F); 0 (M)	↓ (F); 0 (M)	↓
Kim et al. 2017b	2.25	0	0	0
Lamb et al. 2008	1–10	0	0	0
Little et al. 2009	2–12	↓	–	–
Min et al. 2008b	5–13	0	↓	–
Olivero-Verbel et al. 2007	5–9	0	↓	–
Raihan et al. 2018	<2	↓ ^a	↓ ^a	0
Renzetti et al. 2017	4–6	↓	↓	–
Schell et al. 2009	0.5–1	0	↓	–
Yang et al. 2013a	3–9	↓	↓	0

^aAssessments were underweight (defined as weight-for-age z-score <-2) and “stunting” (defined as length-for-age z-score <-2).

↓ = decrease in outcome measure; 0 = no effect on outcome measure; – = not assessed; BMI = body mass index; F = females; M = males

Delayed puberty. Results of studies that evaluated associations between Pb exposure and sexual maturation in boys and girls at child PbB ≤ 10 $\mu\text{g}/\text{dL}$ are summarized in Table 2-44. In girls, delayed onset of puberty, as measured by breast development, pubic hair development, and attainment of menarche, has been corroborated in multiple cross-sectional studies (Den Hond et al. 2011; Denham et al. 2005; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b). Mean PbB in these studies ranged from 0.49 to 4.9 $\mu\text{g}/\text{dL}$. Delays in the predicted attainment of menarche ranged from 3.6 to 10.6 months (Denham et al. 2005; Selevan et al. 2003). Fewer studies examining associations between Pb exposure and sexual maturation in boys at child PbB ≤ 10 $\mu\text{g}/\text{dL}$ are available. Results of these studies are equivocal. Delayed sexual maturation (time to onset to puberty and sexual maturity), measured by genitalia development, testicular volume, and pubic hair development, was observed in three cross-sectional studies of the same study population of 481–489 boys; the median child PbB was 3 $\mu\text{g}/\text{dL}$ at the time of study enrollment (Hauser et al. 2008; Williams et al. 2010, 2019). However, no association between PbB and the onset of puberty was observed in a cross-sectional study of 887 boys with a median PbB of 2.5 $\mu\text{g}/\text{dL}$ (Den Hond et al. 2011).

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Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) $\leq 10 \mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$) ^c	Outcome evaluated	Result ^d
Afeiche et al. 2011 Cross-sectional study; n=999 mother-child pairs	<ul style="list-style-type: none"> Child PbB mean: 3.8 Maternal bone Pb (patella) mean ($\mu\text{g/g}$): 10.4 	Weight (females)	Associations between a 1-SD increase in maternal bone Pb ($\mu\text{g/g}$) and child weight (g) for children aged: <ul style="list-style-type: none"> 12 months: -70.9 (-147.9, 6.0) 24 months: -96.1 (-170.4, -21.8)* 36 months: -121.3 (-200.0, -42.6)* 48 months: -146.4 (-235.5, -57.4)* 60 months: -171.6 (-275.2, -68.0)*
		Weight (males)	Associations between a 1-SD increase in maternal bone Pb ($\mu\text{g/g}$) and child weight (g) for children aged: <ul style="list-style-type: none"> 12 months: 29.4 (-42.1, 100.8) 24 months: 27.8 (-43.5, 99.1) 36 months: 7.9 (-67.3, 83.1) 48 months: -13.6 (-97.9, 70.8) 60 months: -35.0 (-132.4, 62.3)
Alvarez-Ortega et al. 2019 Cross-sectional study; n=554 children (ages 5–16 years)	Mean (SE): 3.5 (0.2) Median: 1.9 Range: 0.1–50.1	Weight	Spearman correlations: <ul style="list-style-type: none"> All participants: -0.152; $p < 0.001$* Females: -0.226; $p < 0.001$* Males: -0.056; $p = 0.380$ Age 5–11 years: -0.069; $p = 0.010$* Age 12–16 years: -0.385; $p < 0.001$*
		Height	Spearman correlations: <ul style="list-style-type: none"> All participants: -0.101; $p = 0.019$* Females: -0.153; $p = 0.009$* Males: -0.037; $p = 0.567$ Age 5–11 years: -0.137; $p = 0.418$ Age 12–16 years: -0.206; $p = 0.009$*

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Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$) ^c	Outcome evaluated	Result ^d
		BMI	Spearman correlations: <ul style="list-style-type: none"> • All participants: -0.172; $p < 0.001^*$ • Females: -0.273; $p < 0.001^*$ • Males: -0.040; $p = 0.536$ • Age 5–11 years: -0.056; $p = 0.295$ • Age 12–16 years: -0.384; $p < 0.001^*$
Dallaire et al. 2014	<ul style="list-style-type: none"> • Cord PbB mean: 4.8 • Child PbB mean: 2.7 	Height	β coefficients (cm per $\mu\text{g/dL}$ cord): -1.57; $p = 0.004^*$
Prospective cohort study; n=290 children (aged 8–14 years)		Head circumference	β coefficients (cm per $\mu\text{g/dL}$ cord): -0.005; $p = 0.04^*$
		Weight	β coefficients (kg per $\mu\text{g/dL}$ cord): β not reported; $p = 0.70$
		BMI	β coefficients (kg/m^2 per $\mu\text{g/dL}$ cord): 0.07; $p = 0.23$
Deierlein et al. 2019	<ul style="list-style-type: none"> • Mean (SD): 1.16 (0.67) • Range: 0.18–5.40 	Height	Predicted mean differences (cm) for PbB ≥ 1 $\mu\text{g/dL}$ compared to < 1 $\mu\text{g/dL}$: <ul style="list-style-type: none"> • Age 7: -2.0 (-3.0, -1.0); $p < 0.001^*$ • Age 14: -1.5 (-2.5, -0.4); $p = 0.01^*$
Prospective longitudinal study; n=of 683 girls (enrolled at ages 6–8 years)		BMI	Predicted mean differences (kg/m^2) for PbB ≥ 1 $\mu\text{g/dL}$ compared to < 1 $\mu\text{g/dL}$: <ul style="list-style-type: none"> • Age 7: -0.7 (-1.2, -0.2); $p = 0.005^*$ • Age 14: -0.8 (-1.5, -0.02); $p = 0.05^*$
		Waist circumference	Predicted mean differences (cm) for PbB ≥ 1 $\mu\text{g/dL}$ compared to < 1 $\mu\text{g/dL}$: <ul style="list-style-type: none"> • Age 7: -2.2 (-3.8, -0.6); $p = 0.01^*$ • Age 14: -2.9 (-4.8, -0.9); $p = 0.005^*$
		Body fat	Predicted mean differences (%) for PbB ≥ 1 $\mu\text{g/dL}$ compared to < 1 $\mu\text{g/dL}$: <ul style="list-style-type: none"> • Age 7: -1.8 (-3.2, -0.4); $p = 0.01^*$ • Age 14: -1.7 (-3.1, -0.4); $p = 0.01^*$

2. HEALTH EFFECTS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$) ^c	Outcome evaluated	Result ^d
Hauser et al. 2008	Child PbB, mean: 3	Height	Regression coefficient (cm per $\mu\text{g/dL}$): -1.439 (-2.25, -0.63); $p < 0.001^*$
Cross-sectional study n=489 children (aged 8–9 years)		Weight	Regression coefficient (kg per $\mu\text{g/dL}$): -0.761 (-1.54, 0.02); $p = 0.067$
		BMI	Regression coefficient (kg/m^2 per $\mu\text{g/dL}$): -0.107 (-0.44, 0.23); $p = 0.53$
		Weight	Weight z score: -0.28 (-0.48, -0.09); $p < 0.05^*$
Hong et al. 2014	Maternal PbB mean: 1.25	Height	Height z score: -0.28 (-0.49, -0.06); $p < 0.05^*$
Cross-sectional study; n=1,150 infants (aged 6–24 months)			
Ignasiak et al. 2006	Child PbB mean: 7.7	Weight	<ul style="list-style-type: none"> Slope boys (kg per \log_{10} $\mu\text{g/dL}$): 4.00 (2.45); $p = 0.10$ Slope girls (kg per \log_{10} $\mu\text{g/dL}$): -6.59 (2.09); $p = 0.001^*$
Cross-section study; n=899 children (aged 7–15 years)		Height	<ul style="list-style-type: none"> Slope boys (cm per \log_{10} $\mu\text{g/dL}$): -6.26 (1.40); $p = 0.002$ Slope girls (cm per \log_{10} $\mu\text{g/dL}$): -5.54 (2.05); $p = 0.007^*$
		BMI	<ul style="list-style-type: none"> Slope boys (kg/m^2 per \log_{10} $\mu\text{g/dL}$): -0.39 (0.82); $p = \text{NS}$ Slope girls (kg/m^2 per \log_{10} $\mu\text{g/dL}$): -1.86 (0.75); $p = 0.01^*$
		Trunk length	<ul style="list-style-type: none"> Slope boys (cm per \log_{10} $\mu\text{g/dL}$): -2.21 (0.97); $p = 0.02^*$ Slope girls (cm per \log_{10} $\mu\text{g/dL}$): -1.47 (1.00); $p = \text{NS}$

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Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Lamb et al. 2008 Population-based prospective cohort; n=309 children (aged 1–10) years	Maternal PbB mean for towns of: • Pristina: 5.60 • Mitrovica: 20.56	Leg length	<ul style="list-style-type: none"> Slope boys (cm per \log_{10} $\mu\text{g}/\text{dL}$): -4.05 (1.27); $p=0.002^*$ Slope girls (cm per \log_{10} $\mu\text{g}/\text{dL}$): -4.08 (1.27) $p=0.0001^*$
		Arm length	<ul style="list-style-type: none"> Slope boys (cm per $\mu\text{g}/\text{dL}$): -3.20 (0.97); $p=0.0001^*$ Slope girls (cm per \log_{10} $\mu\text{g}/\text{dL}$): -2.61 (0.98); $p=0.008^*$
		Trunk-length ratio	<ul style="list-style-type: none"> Slope boys (per \log_{10} $\mu\text{g}/\text{dL}$): 0.71 (0.34); $p=0.04^*$ Slope girls (per \log_{10} $\mu\text{g}/\text{dL}$): 1.03 (0.34); $p=0.003^*$
		Height/BMI	Pristina (β coefficients per \log $\mu\text{g}/\text{dL}$): <ul style="list-style-type: none"> Age 1 year: -0.61 (-2.24, 1.03) Age 10 years: -0.09 (-3.69, 3.52) Mitrovica (β coefficients per \log $\mu\text{g}/\text{dL}$): <ul style="list-style-type: none"> Age 1 year: -0.30 (-2.55, 1.96) Age 10 years: -2.87 (-6.21, 0.47)
Little et al. 2009 Cross-sectional study; n=360 children (aged 2–12 years)	Child PbB mean • 1980 cohort: 23.6 • 2002 cohort: 1.6 • Pooled cohort PbB mean not reported	Height	β coefficient (cm per 10 $\mu\text{g}/\text{dL}$ PbB decrease): 2.1 (1.9, 2.3); $p<0.0001^*$
		Weight	β coefficient (kg per 10 $\mu\text{g}/\text{dL}$ PbB decrease): 1.9 (1.7, 2.1); $p<0.0001^*$
		BMI	β coefficient (kg/m^2 per 10 $\mu\text{g}/\text{dL}$ PbB decrease): 0.5 (0.4, 0.7); $p<0.0001^*$

2. HEALTH EFFECTS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) $\leq 10 \mu\text{g/dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g/dL}$) ^c	Outcome evaluated	Result ^d
Kim et al. 2017b Prospective longitudinal study; n=280 children (18–27 months)	Umbilical cord, mean: 1.31 • All: 1.31 (0.06) • Boys: 1.39 (0.09) • Girls: 1.21 (0.07)	Weight	Regression coefficient β : • 18 months: 0.897 (-0.171, 1.965); p=0.092 • 24 months: 0.717 (0.195, 1.239); p=0.009* • 27 months: 0.316 (-0.345, 0.977); p=0.333
		Height	Regression coefficient β : • 18 months: 0.909 (-0.222, 2.040); p=0.101 • 24 months: 0.138 (-0.530, 0.806); p=0.675 • 27 months: 0.354 (-0.497, 1.205); p=0.394
		BMI	Regression coefficient β : • 18 months: 0.157 (-1.266, 1.580) p=0.806 • 24 months: 0.695 (0.077, 1.313); p=0.029* • 27 months: 0.409 (-0.398, 1.216); p=0.300
Min et al. 2008b Cross-sectional study; n=108 children (aged 5–13 years)	Child PbB mean: 2.4	Height	Regression coefficient cm per $\mu\text{g/dL}$ (SE): -1.449 (0.639); p=0.026*
		Weight	Regression coefficient kg per $\mu\text{g/dL}$ (SE): -0.646 (0.718); 0.370
		BMI	Regression coefficient kg/m^2 per $\mu\text{g/dL}$ (SE): -0.006 (0.272); p=0.982
		Arm length	Regression coefficient cm per $\mu\text{g/dL}$ (SE): -1.804 (0.702); p=0.012*
Olivero-Verbel et al. 2007 Cross-sectional study; n=189 children (aged 5–9 years)	Child PbB mean: 5.53	Height	Correlation coefficient: -0.224; p=0.002*
		Weight	Correlation coefficient: -0.126; p=0.087
Raihan et al. 2018 Cross-sectional study; n=729 children (<2 years of age)	Mean (SD): 8.25 (3.64) 95% CI: 7.98, 8.51 "Normal" PbB: <5 "Elevated" PbB: ≥ 5	Stunting ^e	OR for PbB $\geq 5 \mu\text{g/dL}$ (compared to PbB <5 $\mu\text{g/dL}$): 1.78 (1.07, 2.99); p=0.028*
		Wasting ^e	OR for PbB $\geq 5 \mu\text{g/dL}$ (compared to PbB <5 $\mu\text{g/dL}$): 1.18 (0.64, 2.19); p=0.581
		Underweight ^e	OR for PbB $\geq 5 \mu\text{g/dL}$ (compared to PbB <5 $\mu\text{g/dL}$): 1.63 (1.02, 2.61); p=0.043*

2. HEALTH EFFECTS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Renzetti et al. 2017 Prospective study; n=513 mothers (children assessed at ages 4–6 years)	Maternal PbB (Gmean) <ul style="list-style-type: none"> 2nd trimester: 3.0 (0.8–17.8) 3rd trimester: 3.1 (0.3–28.3) At delivery: 3.5 (0.7–21.9) Umbilical cord: 2.8 (0.4–18.5) 	BMI z-score	β coefficient for: <ul style="list-style-type: none"> 2nd trimester: 0.04 (-0.07, 0.15); p=0.51 3rd trimester: -0.01 (-0.12, 0.10); p=0.81 At delivery: -0.03 (-0.08, 0.14); p=0.58 Cord PbB: 0.05 (-0.08, 0.17); p=0.46
		Percentage body fat	β coefficient for: <ul style="list-style-type: none"> 2nd trimester: -0.13 (-0.75, 0.49); p=0.68 3rd trimester: -0.21 (-0.82, 0.41); p=0.52 At delivery: -0.12 (-0.74, 0.50); p=0.70 Cord PbB: 0.31 (-0.37, 0.99); p=0.37
		Weight-for-age z-score	β coefficient for: <ul style="list-style-type: none"> 2nd trimester: -0.02 (-0.13, 0.09); p=0.68 3rd trimester: -0.11 (-0.22, -0.003); p=0.04* At delivery: -0.03 (-0.13, 0.08); p=0.58 Cord PbB: -0.03 (-0.15, 0.09); p=0.64
		Height-for-age z-score	β coefficient for: <ul style="list-style-type: none"> 2nd trimester: -0.04 (-0.13, 0.04); p=0.32 3rd trimester: -0.10 (-0.19, -0.01); p=0.03* At delivery: -0.04 (-0.13, 0.05); p=0.39 Cord PbB: -0.04 (-0.14, 0.06); p=0.39
Schell et al. 2009 Longitudinal cohort study; n=244 children (aged 3–12 months)	Maternal PbB mean: 2.8	Length	Regression coefficients (SE): <ul style="list-style-type: none"> 6 months (cm per log $\mu\text{g}/\text{dL}$): 0.149 (0.076); p=0.05* 12 months (cm per log $\mu\text{g}/\text{dL}$): 0.073 (0.083); p=0.38
		Weight-for-age	Regression coefficients (SE): <ul style="list-style-type: none"> 6 months (kg per $\mu\text{g}/\text{dL}$): 0.013 (0.098); p=0.89 12 months (kg per $\mu\text{g}/\text{dL}$): 0.124 (0.107); p=0.25

2. HEALTH EFFECTS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Yang et al. 2013a Cross sectional study; n=246 children (aged 3–8 years)	Child PbB mean: 7.30	Weight for length	Regression coefficients (SE): • 6 months(per $\mu\text{g}/\text{dL}$): -0.158 (0.111); p=0.16 • 12 months (per $\mu\text{g}/\text{dL}$): 0.084 (0.111); p=0.45
		Head circumference	Regression coefficients (SE): • 6 months (cm per $\mu\text{g}/\text{dL}$): -0.242 (0.094); p=0.01* • 12 months (cm per $\mu\text{g}/\text{dL}$): -0.220 (0.109); p=0.05*
		Upper arm circumference	Regression coefficients (SE): • 12 months (cm per $\mu\text{g}/\text{dL}$):-0.132 (0.114); p=0.25
		Height	β coefficient(cm per $\mu\text{g}/\text{dL}$): -0.10; p=0.02*
		Weight	β coefficient (kg per $\mu\text{g}/\text{dL}$): -0.14; p=0.01*
		BMI	β coefficient (kg/m ² per $\mu\text{g}/\text{dL}$): -0.08;p=0.24

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 13 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.^cValues are for maternal PbB, unless otherwise specified.^dAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.^eStunting (defined as length-for-age z score <-2), wasting (defined as weight-for-length z-score <-2), and underweight (defined as weight-for-age z-score <-2)

BMI = body mass index; CI = confidence interval; Gmean = geometric mean; NS = not statistically significant; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

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Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL) ^c	Outcome evaluated	Result ^d
Onset of puberty in females			
Den Hond et al. 2011 Cross-sectional study; n=792 girls (aged 14–15 years)	Median: 1.81	Pubic hair development	OR: 0.65 (0.45, 0.93); p=0.020*
Denham et al. 2005 Cross-sectional study; n=138 girls (aged 10–16.9 years)	Mean: 0.49	Attainment of menarche	β coefficient (SE) predicting likelihood of attaining menarche (per ln µg/dL): -1.29 (0.494); p=0.01*
Gollenberg et al. 2010 Cross-sectional study; n=705 girls (aged 6–11 years)	Median: 2.5 Tertiles • T1: <1.0 • T2: 1–4.99 • T3: ≥5.00	Inhibin B pubertal cutoff value	OR for exceeding pubertal cutoff value: • T2 (OR): 0.38 (0.12, 1.15)* • T3 (OR): 0.26 (0.11, 0.60)*
Naicker et al. 2010 Cross-sectional, longitudinal study; n=682 girls (aged 13 years)	Mean: 4.9	Breast development	Trend analysis over ages 8–16 years: p<0.001*
		Pubic hair development	Trend analysis over ages 8–16 years: p<0.001*
		Attainment of menarche	Trend analysis over ages 8–16 years: p<0.001*

2. HEALTH EFFECTS

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤ 10 $\mu\text{g}/\text{dL}$ ^a

Reference and study population ^b	PbB ($\mu\text{g}/\text{dL}$) ^c	Outcome evaluated	Result ^d
Selevan et al. 2003	Gmean	Breast development	<ul style="list-style-type: none"> NHW OR: 0.82 (0.47, 1.42) NHAA OR: 0.64 (0.42, 0.97); $p < 0.05^*$ MA OR: 0.76 (0.63, 0.91); $p < 0.05^*$
Cross-sectional study; n=2,186 girls (aged 8–18 years)	<ul style="list-style-type: none"> NHW: 1.4 NHAA: 2.1 MA: 1.7 	Pubic hair development	<ul style="list-style-type: none"> NHW OR: 0.75 (0.37, 1.51) NHAA OR: 0.62 (0.41, 0.96); $p < 0.05$ MA OR: 0.70 (0.54, 0.91); $p < 0.05$
		Age of menarche	<ul style="list-style-type: none"> NHW HR: 0.74 (0.55, 1.002) NHAA HR: 0.78 (0.63, 0.98); $p < 0.05$ (age at menarche delayed 3.6 months)* MA HR: 0.90 (0.73, 1.11)
Wolff et al. 2008	Median: 2.4	Breast development	PR for breast stage ≥ 2 versus stage 1: 1.01 (0.79, 1.30)
Cross-sectional study; n=192 girls (aged 9 years)		Pubic hair development	PR for pubic hair stage ≥ 2 versus stage 1: 1.25 (0.83, 1.88)
Wu et al. 2003b	Mean: 2.5 Tertiles:	Breast development	<ul style="list-style-type: none"> OR for T2: 1.51 (0.90, 2.53) OR for T3: 1.20 (0.51, 2.85)
Cross-sectional study; n=1,706 girls (aged 8–16 years)	<ul style="list-style-type: none"> T1: 0.7–2.0 (reference) T2: 2.1–4.9 T3: 5.0–21.7 	Pubic hair development	<ul style="list-style-type: none"> OR for T2: 0.48 (0.25, 0.92)* OR for T3: 0.27 (0.08, 0.93)*
		Attainment of menarche	<ul style="list-style-type: none"> OR for T2: 0.42 (0.18, 0.97)* OR for T3: 0.19 (0.08, 0.43)*

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Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL) ^c	Outcome evaluated	Result ^d
Onset of puberty in males			
Den Hond et al. 2011	Median: 2.50	Onset of puberty	No association between PbB and the onset of puberty (specific data not reported)
Cross-sectional study; n=887 boys (aged 12–15 years)			
Hauser et al. 2008	Median: 3	Genitalia development	OR for having entered genitalia stage G2 for PbB ≥5 compared to PbB <5: 0.57 (0.34, 0.95); p=0.03*
Cross-sectional study; n=489 peripubertal boys (aged 8–9 years)			
Williams et al. 2010	Median: 3	Testicular volume	HR for testicular volume <3 mL for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.73 (0.55, 0.97); p=0.03*
Longitudinal cohort; n=489 peripubertal boys (aged 8–9 years)			
		Genitalia stage	HR for having entered genitalia stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.76 (0.59, 0.98); p=0.04*
		Pubic hair stage	HR for having entered pubic hair stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.69 (0.44, 1.07); p=0.10

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Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL^a

Reference and study population ^b	PbB (µg/dL) ^c	Outcome evaluated	Result ^d
Williams et al. 2019 Longitudinal cohort; n=481 boys (enrolled at ages 8–9 years)	Median: 3	Onset of puberty	Difference in age (shift in mean age in months) (95% CI) for PbB ≥5 µg/dL compared to PbB, based on: <ul style="list-style-type: none"> • Genitalia: 8.40 (3.70, 13.10); p<0.001* • Pubic hair: 8.12(3.46, 12.78); p<0.001* • Testicular volume: 7.68 (3.46, 11.90); p<0.001*
		Onset of sexual maturity	Difference in age (shift in mean age in months) (95% CI) for PbB ≥5 µg/dL compared to PbB, based on: <ul style="list-style-type: none"> • Genitalia: 4.20 (0.56, 7.84); p=0.024* • Pubic hair: 4.23 (-0.31, 8.77); p=0.068 • Testicular volume: 5.14 (1.70, 8.58); p=0.003*

^aSee the *Supporting Document for Epidemiological Studies for Lead*, Table 13 for more detailed descriptions of studies.^bParticipants had no known occupational exposure to Pb.^cValues are for maternal PbB, unless otherwise specified.^dAsterisk and bold indicate association with Pb, unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table

CI = confidence interval; Gmean = geometric mean; HR = hazard ratio; MA = Mexican Americans; NHW = Non-Hispanic whites; NHAA = Non-Hispanic African Americans; OR = odds ratio; Pb = lead; PR = prevalence ratio; SE = standard error

2. HEALTH EFFECTS

Associations Between Bone Pb and Birth Outcome and Postnatal Growth. Studies evaluating associations between maternal bone Pb and birth outcome (birth weight and length, head circumference) and postnatal growth (infant and child weight gain) are summarized in Table 2-45. Studies were conducted in mother-infant/child pairs residing in Mexico City. Maternal tibia Pb was inversely associated with birth weight (Cantonwine et al. 2010; González-Cossío; Kordas et al. 2009), birth length (Hernandez-Avila et al. 2002), and head circumference (Hernandez-Avila et al. 2002; Kordas et al. 2009). Maternal patella Pb was associated with decreased head circumference (Hernandez-Avila et al. 2002), but not birth weight (Afeiche et al. 2011; González-Cossío) or birth length (Hernandez-Avila et al. 2002). Infant weight gain measured at 1 month of age was inversely associated with maternal patella Pb, but not maternal tibia Pb (Sanin et al. 2001); no associations between maternal tibia or patella Pb were observed from birth to 12 months of age (Afeiche et al. 2011). Maternal patella Pb was inversely associated with weight gain in girls, but not boys, at 5 years of age; however, no associations were observed for maternal tibia Pb for boys or girls. In contrast, no associations were observed in a prospective study examining the relationships between maternal patella or tibia Pb (measured 1 month postpartum) and BMI, percent body fat, weight-for-age score, or height-for-age score in children ages 4–6 years (Renzetti et al. 2017). Taken together, results of these studies provide evidence that long-term maternal Pb exposure is inversely associated with infant size and post-natal growth.

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

Reference	Population ^a	Effect				
		Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain
Afeiche et al. 2011	Mother-infant pairs (522 boys; 477 girls)	0 T (M, F) 0 P (M, F)	–	–	0 T (M, F) ^b 0 P (M, F) ^b	0 T (M, F) 0 P (M) ↓ P (F) ^c
Cantonwine et al. 2010	538 mother-infant pairs	↓ T	–	–	–	–
Gonzalez-Cossio et al. 1997	272 mother-infant pairs	↓ T 0 P	–	–	–	–
Hernandez-Avila et al. 2002	223 mother-infant pairs	–	↓ T 0 P	↓ T ↓ P	–	–
Kordas et al. 2009	474 mother-infant pairs	↓ T	0 T	↓ T	–	–

2. HEALTH EFFECTS

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

Reference	Population ^a	Effect				
		Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain
Renzetti et al. 2017	424 (P) and 430 (T) mother-child pairs	–	–	–	–	0 T ^d 0 P ^d
Sanin et al. 2001	329 mother-infant pairs	–	–	–	0 T ^e ↓ P ^e	–

^aFrom Mexico City.^bMeasured from birth to 12 months of age.^cMeasured at 5 years of age.^dMeasured at 4–6 years; assessments included BMI, percentage body fat, weight-for-age, and height-for-age. No associations between maternal Pb and any of the assessments were observed.^eMeasured at 1 month of age.

↓ = inverse association; 0 = no association; – = not reported; F = female; M = male; P = patella; Pb = lead; T = tibia

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in adverse development effects. EPA (2014c) specifically noted that delayed puberty may result from alterations in pulsatile release of sex hormones and that insulin-like growth factor 1 (IGF-1) may play a role in this effect. Pb is distributed to the fetus and has been measured in umbilical cord blood, placenta, and follicular fluid (See Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct exposure of the fetus.

2.19 CANCER

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and cancer. Studies include exposure of workers and general populations, with many studies reporting PbB. In most studies, mean PbBs in these studies are <10 µg/dL. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent and interpretation may be limited due to confounding factors.

Many studies of occupational cohorts and cancer risks do not report PbB data. These studies have reported associations between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder. However, results are inconsistent and interpretation may be limited due to confounding factors.

The following cancers have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Increased risk of all cancer; evaluated in multiple studies with mixed results.
 - Increased risk of lung cancer; evaluated in multiple studies with mixed results.
- >10 $\mu\text{g/dL}$:
 - Increased risk of all cancer; evaluated in multiple studies with mixed results.
 - Increased risk of respiratory tract cancers (bronchus, trachea, lung); evaluated in multiple studies with mixed results.
 - Increased risk of stomach cancer; evaluated in multiple studies with mixed results.
 - Increased risk of intestinal cancer.
 - Increased risk of cancer of the larynx.
 - Increased risk of glioma.

Carcinogenicity Classifications of Pb and Pb Compounds. IARC has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006). The National Toxicology Program 14th Report on Carcinogens classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). As the basis of the Group 2A classification for inorganic Pb compounds, IARC (2006) cited multiple animal studies showing kidney cancer following chronic oral and parenteral exposure (Azar et al. 1973; Balo et al. 1965; Fears et al. 1989; Kasprzak et al. 1985; Koller et al. 1985; Van Esch and Kroes 1969; Zawirska 1981; Zollinger 1953), renal tubular adenoma in offspring of mice exposed during gestation and lactation (Waalkes et al. 1995), and brain gliomas following oral exposure of rats (Zawirska 1981; Zawirska and Medras 1972). For epidemiological studies of occupational cohorts, IARC (2006) noted limited evidence of carcinogenicity of the lung, stomach, kidney, and brain/nervous system, although studies yielded inconsistent results, and interpretation of results was compromised due to potential confounding factors (e.g., smoking, occupational exposure to other carcinogens such as arsenic).

Confounding Factors and Effect Modifiers. Numerous factors can influence results of epidemiological studies evaluating associations between Pb exposure and cancer, including smoking status, family history of cancer, and co-exposure to other carcinogens. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of

the effect of the variable on the outcome. For example, many occupational studies include smelters where exposure to arsenic and other carcinogenic metals (e.g., cadmium) can be correlated with exposure to Pb. Exposures to Pb occur throughout the lifetime and a cross-sectional evaluation of PbB may not adequately represent the exposure history of the individual.

Measures of Exposure. Numerous studies evaluating cancer in general populations and Pb-exposed workers report PbB as a measure of exposure. A few studies measured exposure by bone Pb concentrations, cumulative blood Pb index, or cumulative exposure (Bhatti et al. 2009; Englyst et al. 2001; Ionescu et al. 2007; Rajaraman et al. 2006); however, these studies did not report PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and cancer. Studies of general populations and workers are briefly summarized in Table 2-46. Studies of general populations include large cross-sectional studies (n=5,482–13,946) of NHANES participants (Cheung et al. 2013; Jemal et al. 2002; Menke et al. 2013; Schober et al. 2006). Mean PbBs in most studies are <10 µg/dL, although in some studies that stratify by PbB, the highest exposure categories are >10 µg/dL (Jemal et al. 2002; Kelly et al. 2013; Schober et al. 2006). Results of two studies with PbB <10 µg/dL show increased risks of all cancer and of lung cancer (Cheung et al. 2013; Schober et al. 2006), although other studies show no increases in cancer risk (Jemal et al. 2002; Khalil et al. 2009; Kelly et al. 2013; Menke et al. 2013; Santibanez et al. 2008; Wiesskopf et al. 2009). Results of occupational exposure studies are mixed and do not establish a pattern of effects of exposure-response relationships. PbBs in these studies generally are >40 µg/dL. Studies have reported associations between PbB and all cancers (Anttila et al. 1995; Lundstrom et al. 1997; Lustberg and Silbergeld 2002; McElvenny et al. 2015; Wong and Harris et al. 2000), cancers of the bronchus, trachea, and lung (Anttila et al. 1995; Barry and Steenland 2019; Chowdhury et al. 2014; Kim et al. 2015; Lundstrom et al. 1997; McElvenny et al. 2015; Steenland and Boffetta 2000; Steenland et al. 2017, 2019), cancer of the larynx (Barry and Steenland 2019; Chowdhury et al. 2014; Steenland et al. 2019), esophageal cancer (Steenland et al. 2019), stomach cancer (Cooper et al. 1985; Steenland and Boffetta 2000; Steenland et al. 2017, 2019; Wong and Harris et al. 2000), intestinal or rectal cancer (Kim et al. 2015; Steenland et al. 2019), bladder cancer (Steenland et al. 2017), and gliomas (Anttila et al. 1996).

Many studies of occupational cohorts with high exposure to Pb and cancer risks do not report PbB data (Bertazzi and Zocchetti 1980; Bhatti et al. 2009; Cocco et al. 1994, 1997, 1998a, 1998b, 1999a, 1999b; Davies 1984a, 1984b; Dingwall-Fordyce and Lane 1963; Fayerweather et al. 1997; Hu et al. 1999; Jones et al. 2007; Kauppinen et al. 1992; Lin et al. 2009; McElroy et al. 2008; Michaels et al. 1991; Pan et al.

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Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects ^a
General population			
Cheung et al. 2013	Mean (SE): 4.44 (0.14)	All cancer	OR: 1.071 (1.036, 1.106)*
Cross-sectional study; n=3,482 (NHANES III)		Lung cancer	OR: 1.090 (1.054, 1.127)*
Jemal et al. 2002	Quartiles: • Q1: ≤9.8 • Q2: 9.9–12.9 • Q3: 13.0–16.9 • Q4: ≥17.0	All cancer	Adjusted RR Q4: 1.50 (0.75, 3.01)
Cross-sectional study; n=3,592 (NHANES II, age 6 months–74 years)			
Khalil et al. 2009	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All cancer	Adjusted HR PbB ≥8 (versus <8): 1.64 (0.73, 3.71)
Prospective cohort study; n=532 women (age 65–87 years)			
Kelly et al. 2013	Mean (range) • Males: 6.18 (1.54, 67.2) • Females: 5.27 (1.1, 40.1)	NHL	OR Q4: 0.93 (0.43, 2.02) p-trend=0.849
Nested case-control study; n=194 cases NHL; 76 cases MM; and 270 controls (mean age 53.08 years)	Quartiles • Q1: 1.5423–3.986 • Q2: 3.9504–5.8763 • Q3: 5.8832–8.7218 • Q4: 8.7531–40.0843	MM	OR Q4: 1.63 (0.45, 5.94) p-trend=0.533
Menke et al. 2006	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.62	All cancer	Adjusted OR • T2: 0.72 (0.46, 1.12); p-trend=0.130 • T3: 1.10 (0.82, 1.47); p-trend=0.101
Cross-sectional study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)			
Santibanez et al. 2008	Low: ≤4.9 High: >4.9	Esophageal	Adjusted OR • Low: 0.79 (0.43, 1.46) • High: 1.69 (0.57, 5.03)
Case-control study; n=185 esophageal cancer patients; 285 controls (age 30–80 years)			

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Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects ^a
Schober et al. 2006			
Cross-sectional study; n=9,757 (NHANES III; age ≥40 years)	Tertiles <ul style="list-style-type: none"> • T1: <5 (mean 2.6) • T2: 5–9 (mean 6.3) • T3: >10 (mean 11.8) 	All cancer	Adjusted RR <ul style="list-style-type: none"> • T2: 1.44 (1.12, 1.86)* • T3: 1.69 (1.14, 2.52)* • p-trend<0.01*
Weisskopf et al. 2009	Mean (SD): 5.6 (3.4) Tertiles: <ul style="list-style-type: none"> • T1: <4 • T2: 4–6 • T3: >6 	All cancer	Adjusted HR T3: 0.48 (0.25–0.91)*; p-trend=0.02
Prospective study; n=868 men (Normative Aging Study; age 21–80 years)			
Workers			
Anttila et al. 1995			
Cross-sectional study; n=20,700 workers (age 30–74 years)	Tertiles: <ul style="list-style-type: none"> • T1: 0–18.6 • T2: 20.7–39.4 • T3: 41.1–161.6 	All cancer	SMR T2: 1.4 (1.1, 1.8)* SMR T3: 1.2 (0.9, 1.8)
		Lung, trachea	SMR T2: 2.0 (1.2, 3.2)* SMR T3: 1.5 (0.8, 2.1)
Anttila et al. 1996			
Cross-sectional study; n=20,741 workers (age 18–74 years)	Tertiles: <ul style="list-style-type: none"> • T1: 2.1–14.5 • T2: 16.6–26.9 • T3: 29.0–89.1 	All nervous system cancers	Adjusted OR T3: 2.2 (0.7, 6.6) p-trend=0.17
		Glioma	Adjusted OR T3: 11 (1.0, 626)* p-trend: 0.037

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Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects ^a
Barry and Steenland 2019			
	Quartiles		
	• Q1: 0-<5	Colon	HR Q4: 1.19 (0.54, 2.61)
Retrospective study; n=58,368 male workers (follow-up of Chowdhury et al. 2014)	• Q2: 5-<25	Esophagus	HR Q4: 0.97 (0.43, 2.20)
	• Q3: 25-<40	Kidney	HR Q4: 0.92 (0.32, 2.58)
	• Q4: ≥40	Liver	HR Q4: 1.53 (0.79, 2.99)
		Lung	HR Q2: 1.61 (1.04, 2.48)* HR Q3: 2.03 (1.34, 3.10)* HR Q4: 2.92 (1.91, 4.46)* p-trend: <0.01*
		Stomach	HR Q4: 0.64 (0.22, 1.82)
		Brain	HR Q4: 1.49 (0.71, 3.12)
		Bladder	HR Q4: 1.71 (0.83, 3.55)
		Larynx	HR Q4: 3.42 (1.29, 9.09)*
		Non-Hodgkin's lymphoma	HR Q4: 1.60 (0.85, 3.01)
		Pancreas	HR Q4: 1.15 (0.72, 1.85)
		Rectal	HR Q4: 2.06 (0.87, 4.84)
Chowdhury et al. 2014			
	Quartiles	Lung	SMR Q4: 1.20 (1.03, 1.39)*
	• Q1: 0-<5	Brain	SMR Q4: 0.83 (0.41, 1.49)
	• Q2: 5-<25	Kidney	SMR Q4: 0.72 (0.33, 1.37)
	• Q3: 25-<40	Stomach	SMR Q4: 0.92 (0.44, 1.69)
	• Q4: ≥40	Esophagus	SMR Q4: 0.65 (0.32, 1.16)
		Larynx	SMR Q4: 2.11 (1.05, 3.77)*
		Bladder	SMR Q4: 0.70 (0.28, 1.45)
Cooper et al. 1985			
	Mean	All cancer	Battery PMR: 1.06 (0.96, 1.16) Smelters PMR: 1.02 (0.87, 1.19)
Cohort study; n=4,519 battery workers; 2,300 smelters	• Battery (n=1,326): 62.7 • Smelters (n=537): 79.7	Stomach	Battery PMR: 1.54 (1.11, 2.15)* Smelters PMR: 1.03 (0.75, 1.42)
		Large intestine	Battery PMR: 0.98 (0.69, 1.40) Smelters PMR: 1.19 (0.62, 2.28)

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Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects ^a
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean (SD) <ul style="list-style-type: none"> • Males: 8.8 (8.5) • Females 5.8 (5.4) Tertiles: <ul style="list-style-type: none"> • T1: <10 • T2: 10–20 • T3: >20 	Larynx	Battery PMR: 1.19 (0.54, 2.65) Smelters PMR (95% CI): 1.06 (0.27, 4.21)
		Bronchus, trachea, lung	Battery PMR: 1.16 (0.97, 1.39) Smelters PMR: 1.13 (0.84, 1.51)
		Brain and other CNS	Battery PMR: 1.09 (0.55, 2.18) Smelters PMR: 0.97 (0.32, 3.01)
		All cancer	Males: RR T3: 0.95 (0.56, 1.61) Females RR T3: 1.68 (0.40, 7.13)
		Stomach	Males: RR T3: 0.80 (0.23, 2.71) Females RR T2: 1.82 (0.20, 16.36) Females T3: no cases
		Colo-rectal	Males: RR T3: 1.86 (0.35, 9.79) Females RR T2: 13.42 (1.21, 149.4)*; p<0.05 Females T3: no cases
		Liver	Males: RR T3: 1.72 (0.72, 4.14) Females T2 RR: 0.83 (0.10, 6.56) Females T3: no cases
		Bronchus, lung	Males: RR T3: 0.46 (0.10, 2.01) Females RR T2: 10.45 (1.74, 62.93)*; p<0.05 Females RR T3: 12.68 (1.69, 147.86)*; p<0.05
		All cancer	SMR: 1.2 (1.0, 1.5)*
		Lung	SMR: 2.8 (2.0, 3.8)*
Lundstrom et al. 1997	Mean:		
Cross-sectional study; n=3979 workers	• In 1950: 62.2		
	• In 1987: 33.2		
Lundstrom et al. 2006	Peak:		
Nested case-referent study; 3,979 smelter workers	Cases (n=40): 49.7		
	Referents (n=114): 55.9		
		Lung	OR: 0.93 (0.60, 1.44)

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Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects ^a
Lustberg and Silbergeld 2002	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All cancer (rate ratio)	RR T2: 1.46 (0.87, 2.48) RR T3: 1.68 (1.02, 2.78)*
Cross-sectional study; n=4,292; age 30–74 years (NHANES II)			
McElvenny et al. 2015	Mean (SD): 44.3 (22.7) Range: 2.3–321.5	All cancer	SMR: 1.13 (1.07, 1.20)*
Cohort study; n=9,122 workers; mean age 29.2 years		Esophagus	SMR: 1.05 (0.78, 13.8)
		Stomach	SMR: 1.11 (0.86, 1.43)
		Colon	SMR: 0.98 (0.77, 1.26)
		Kidney	SMR: 1.30 (0.91, 1.86)
		Bladder	SMR: 0.95 (0.67, 1.35)
		Bronchus, trachea, lung	SMR: 1.42 (1.29, 1.57)*
		Brain	SMR: 0.92 (0.61, 1.38)
Selevan et al. 1985	Mean: 56.3	All cancer	SMR: 0.95 (0.78, 1.14)
Retrospective cohort study; n=1,987 male workers		Digestive organs	SMR: 0.77 (0.52, 1.10)
		Respiratory system	SMR: 1.11 (0.80, 1.51)
		Kidney	SMR: 2.04 (0.75, 4.44)
		Bladder	SMR: 1.44 (0.53, 3.14)
Steenland and Boffetta 2000	Range of study means: 26–80	Lung	RR: 1.14 (1.04, 1.25)*
Meta-analysis; data from eight studies on Pb workers; n=36,027 workers		Stomach	RR: 1.34 (1.14, 1.57)*
		Brain	RR: 1.06 (0.81, 1.40)
Steenland et al. 1992	Mean: 56.3	All Cancer	SMR: 0.98 (0.84, 1.12)
Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers		Colon	SMR: 0.48 (0.22, 0.90)
		Lung	SMR: 1.18 (0.92, 1.48)
		Kidney	SMR: 1.93 (0.88, 3.67)

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Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects ^a
Steenland et al. 2017	Median: 26	Bladder (>40 µg/dL)	HR: 1.86 (1.04, 3.33)*
Cohort study; n=88,000 Pb workers		Kidney (>40 µg/dL)	HR: 1.21 (0.74, 1.97)
		Larynx (>40 µg/dL)	HR: 2.69 (1.07, 6.76)*
		Lung (20–<30 µg/dL)	HR: 1.39 (1.19, 1.64)*
		Stomach (20–<40 µg/dL)	HR: 1.62 (1.13, 2.32)*
		Brain (>40 µg/dL)	HR: 1.71 (0.94, 3.12)
Steenland et al. 2019	Median: 29	Bladder (>40 µg/dL)	HR: 1.24 (0.87, 1.75)
		Esophagus (30–39 µg/dL)	HR: 2.00 (1.08, 3.71)*
		Kidney (>40 µg/dL)	HR: 1.00 (0.66, 1.51)
		Larynx (>40 µg/dL)	HR: 1.92 (0.94, 3.91)
		Lung (20–29 µg/dL)	HR: 1.39 (1.17, 1.65)*
		Rectum (>40 µg/dL)	HR: 1.49 (1.03, 2.17)*
		Stomach (20–29 µg/dL)	HR: 1.55 (1.10, 2.18)*
		All cancer	SMR: 1.045 (1.012, 1.080)*
Wong and Harris et al. 2000	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	Stomach	SMR: 1.474 (1.125, 1.898)*
		Large intestine	SMR: 0.994 (0.789, 1.235)
		Bronchus, trachea, lung	SMR: 1.164 (1.039, 1.299)
		Kidney	SMR: 0.636 (0.339, 1.087)
		CNS	SMR: 0.748 (0.419, 1.234)

^aAsterisk and bold indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; MM = multiple myeloma; NHANES = National Health and Nutrition Examination Survey; NHL = non-Hodgkin's lymphoma; OR = odds ratio; Pb = lead; PMR = proportionate mortality ratio; RR = rate ratio or relative ratio; SD = standard deviation; SE = standard error; SMR = standard mortality ratio

2011; Partanen et al. 1991; Pesch et al. 2000; Rajaraman et al. 2006; Risch et al. 1988; Rousseau et al. 2007; Sankila et al. 1990; Sheffet et al. 1982; Siemiatycki 1991; Sweeney et al. 1986; van Wijngaarden and Dosemeci 2006; Wingren and Englander 1990). Although results of these studies are mixed and interpretation may be limited due to confounding factors, associations have been reported between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder.

Mechanisms of Action. Numerous mechanisms for Pb-induced carcinogenicity have been proposed (EPA 2014c); however, it is likely that a combination of mechanisms, rather than a single mechanism, is involved. Although Pb is considered to be only weakly mutagenic, it has been shown to produce DNA damage (single and double strand breaks), sister chromatid exchanges (SCEs), chromosome aberrations, micronuclei (MN) formation, and cytogenetic damage. Epigenetic mechanisms (e.g., changes in gene expression in the absence of changes to DNA), post-translational alterations to protein structure, and immune modulation of tumorigenesis in response to Pb-induced ROS oxidative damage and inflammation have also been proposed as possible mechanisms involved in Pb-induced carcinogenesis.

2.20 GENOTOXICITY

The genotoxicity of Pb has been studied in Pb workers and the general population, in *in vivo* animal models, and *in vitro* cultures of microorganisms and mammalian cells. For the following discussions, data from epidemiological studies on genotoxicity were obtained from the primary literature. Information on *in vitro* studies and *in vivo* animal studies was taken from comprehensive reviews of Pb genotoxicity (EPA 2014c; Garcia-Leston et al. 2010; IARC 2006; NTP 2003).

Epidemiological Studies

Overview. Epidemiological studies have examined genotoxic effects associated with Pb exposure in adults (general populations and workers) and children. Most studies were conducted in small populations of workers. Numerous studies with PbB ≥ 10 $\mu\text{g/dL}$ report associations for exposure to Pb and genotoxic endpoints (gene mutation, DNA damage, SCE, MN formation, and DNA methylation), although some inverse associations have been reported. Few epidemiology studies have evaluated genotoxicity at PbB ≤ 10 $\mu\text{g/dL}$.

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The following genotoxic effects have been associated with PbB:

- ≤ 10 $\mu\text{g/dL}$:
 - Gene mutation.
 - DNA damage; evaluated in a few studies with mixed results.
 - DNA methylation; positive results, corroborated in a few studies.
- > 10 $\mu\text{g/dL}$:
 - DNA damage; corroborated in numerous studies.
 - Decreased telomere length.
 - Chromosomal aberrations; evaluated in numerous studies with mainly positive results.
 - Sister chromatid exchange; evaluated in numerous studies with mainly positive results.
 - Micronuclei formation; evaluated in numerous studies with mainly positive results.
 - DNA methylation.

Measures of Exposure. Studies evaluating the association between genotoxic effects and Pb exposure typically evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies evaluating genotoxic effects were conducted in worker populations. Therefore, potential co-exposure to other genotoxic compounds (such as arsenic) could occur, complicating interpretation of results. In addition, many studies were conducted in small populations ($n < 100$). Variable outcomes of genotoxicity studies in human populations may derive from the influence of experimental variables that may act as confounders, such as duration and route of Pb exposure, cell culturing time following the exposure, smoking habits, and simultaneous exposure to other toxic agents that could act by modifying the genotoxic response of the cells to Pb exposure and similarly, modifying the results of the studies (García-Lestón et al. 2010).

Characterization of Effects. General trends for studies demonstrating associations between PbB and genotoxic effects are shown in Table 2-47. Additional study details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 14. Although few studies have evaluated genotoxic effects at $\text{PbB} \leq 10$ $\mu\text{g/dL}$ (see discussion below), numerous studies in adult workers with mean PbBs ranging from 20 to > 50 $\mu\text{g/dL}$ provide evidence of increased DNA damage, chromosomal aberrations, SCEs, and MN. One study reported decreased telomere length in workers (Pawlas et al. 2016). A few studies in workers reported negative findings for chromosomal aberrations (Anwar and Kamal 1988; Bulsma and DeFrance 1976; Mäki-Paakkanen et al. 1981; Schwanitz et al. 1975) and SCEs

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(Grandjean et al. 1983; Mäki-Paakkanen et al. 1981); however, positive results for these endpoints were reported in other studies at similar PbBs.

Table 2-47. Overview of Epidemiology Studies Evaluating Genotoxicity Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Gene mutation	Van Larebeke et al. 2004
	DNA damage/repair	Akram et al. 2019; Jasso-Pineda et al. 2012;
	Decreased telomere length	Pawlas et al. 2015
	MN	Mielzynska et al. 2006; Wu et al. 2017
	DNA methylation	Hanna et al. 2012; Li et al. 2016b; Pilsner et al. 2009
>10–30	DNA damage/repair	Chinde et al. 2014; Danadevi et al. 2003; Dobrakowski et al. 2017; Jannuzzi and Alpertunga 2016; Kašuba et al. 2012; Kayaalti et al. 2015b; Méndez-Gómez et al. 2008; Shaik and Jamil 2009
	Chromosomal aberrations	Pinto et al. 2000
	SCE	Anwar and Kamal 1988; Pinto et al. 2000
	MN	Chinde et al. 2014; Khan et al. 2010b; Kašuba et al. 2012; Nordenson et al. 1978; Pinto et al. 2000
>30–50	DNA damage/repair	Dobrakowski et al. 2017; Fracasso et al. 2002; Grover et al. 2010; Pawlas et al. 2017
	Decreased telomere length	Pawlas et al. 2016
	Chromosomal aberrations	Forni et al. 1976; Grover et al. 2010; Schwanitz et al. 1970
	SCE	Duydu et al. 2001, 2005; Wiwanitkit et al. 2008; Wu et al. 2002
	MN	Grover et al. 2010; Hamurcu et al. 2001; Minozzo et al. 2004
	DNA methylation	Devoz et al. 2017
>50	DNA damage/repair	de Restrepo et al. 2000
	Chromosomal aberrations	Al-Hakkak et al. 1986; Forni et al. 1976; Huang et al. 1988; Nordenson et al. 1978; Schwanitz et al. 1970
	SCE	Huang et al. 1988
	MN	Shaik and Jamil 2009; Singh et al. 2013; Vaglenov et al. 1998, 2001

DNA = deoxyribonucleic acid; MN = micronuclei; PbB = blood lead concentration; SCE = sister chromatid exchange

Results of genotoxicity studies conducted in small populations of children (n=12–103) are inconsistent; for study details, see the *Supporting Document for Epidemiological Studies for Lead*, Table 14. Mixed results were observed for studies on DNA damage, with positive associations at mean PbBs of 7.3 and 28.5 µg/dL (Méndez-Gómez et al. 2008; Jasso-Pineda et al. 2012) and no associations at a mean PbB of 19.5 µg/dL (Méndez-Gómez et al. 2008). No associations were observed for chromosome aberrations at

a PbB range of 12–33 µg/dL (Bauchinger et al. 1977) and for SCE at mean PbBs of 7.69 and 62.7 µg/dL (Dalpra et al. 1983; Mielzynska et al. 2006). MN formation was positively associated with a mean PbB of 7.69 µg/dL (Mielzynska et al. 2006), and altered DNA methylation was found in newborns at mean umbilical cord PbB of 6.6 µg/dL (Pilsner et al. 2009) and mean prenatal maternal RBC Pb of 1.2 µg/dL (Wu et al. 2017).

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating genotoxic effects of PbB ≤10 µg/dL are summarized in Table 2-48, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 14. Few studies have evaluated genotoxicity at PbB ≤10 µg/dL. Some endpoints were only evaluated in a single study; therefore, it is difficult to draw conclusions. With the exception of a large study conducted in NHANES participants (Zota et al. 2015), genotoxic effects were evaluated in small study populations (n=12–103). Gene mutations were observed in a single study of Finnish women at a PbB range of 1.6–5.2 µg/dL (Van Larebeke et al. 2004). Results of studies on DNA damage are mixed, with no associations in adult workers at PbB means of 2.1–4.4 µg/dL (Al Bakheet et al. 2013; Hengstler et al. 2003), and positive associations in a small study of children with a mean PbB of 7.3 µg/dL (Jasso-Pineda et al. 2012). No effect on telomere length was observed in a large NHANES study of adults with a mean PbB of 1.67 µg/dL (Zota et al. 2015). No associations were observed for SCE in a single study in workers with a mean PbB of 9.3 µg/dL and for MN in children with a mean PbB of 7.69 µg/dL (Mielzyńska et al. 2006; Wu et al. 2002). Studies on DNA methylation showed positive associations in adult women undergoing *in vitro* fertilization (median PbB 2.88 µg/dL), in children (mean PbB: 1.36 µg/dL), and in newborns (mean umbilical cord PbB 6.6 µg/dL or prenatal maternal RBC Pb 1.2 µg/dL) (Hanna et al. 2012; Li et al. 2016b; Pilsner et al. 2009; Wu et al. 2017).

In Vivo Animal Models and In Vitro Cultures of Mammalian Cells and Microorganisms. Numerous studies have investigated the genotoxicity of Pb using *in vivo* animal models and cultured mammalian cells and microorganisms. Rather than reviewing these numerous studies, an overview of findings is summarized below. This information was taken from the following reviews: EPA 2006, 2014c; IARC 2006; NTP 2016.

In vivo studies in animals. DNA damage has been observed in several *in vivo* exposure studies in rodents. DNA damage (single strand breaks), as measured in comet assays, was observed in various organ systems, bone marrow, leukocytes, and spermatozoa of mice and rats following repeated inhalation or oral exposures to Pb or Pb acetate. Many of these studies administered Pb by parenteral routes (intravenous, intraperitoneal). Narayana and Al-Bader (2011) and Narayana and Raghupathy (2012) did

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Table 2-48. Results of Genotoxicity Studies at Blood Lead Concentration (PbB) ≤10 µg/dL

PbB or range (µg/dL)	Population (n)	Gene mutation	DNA damage	Telomere length	SCE	MN	DNA methylation	Reference
1.6–5.2	Women (99)	↑	NA	NA	NA	NA	NA	Van Larebeke et al. 2004
2.1	Men (40)	NA	0	NA	NA	NA	NA	Al Bakheet et al. 2013
3.28	Children (99)	NA	NA	↓	NA	NA	NA	Pawlas et al. 2015
4.4	Workers (78)	NA	0	NA	NA	NA	NA	Hengstler et al. 2003
7.3	Children (12)	NA	↑	NA	NA	NA	NA	Jasso-Pineda et al. 2012
1.67	Adults (6,796) ^a	NA	NA	0	NA	NA	NA	Zota et al. 2015
9.3	Workers (34)	NA	NA	NA	0	NA	NA	Wu et al. 2002
7.69	Children	NA	NA	NA	NA	0	NA	Mielzyńska et al. 2006
>0.73	Women (43)	NA	NA	NA	NA	NA	↓	Hanna et al. 2012
1.45	Adults (78) ^b	NA	NA	NA	NA	NA	↓	Li et al. 2016b
6.6 ^c	Newborns (103)	NA	NA	NA	NA	NA	↑↓	Pilsner et al. 2009
8	Workers (100)	NA	↑	NA	NA	NA	NA	Akram et al. 2019
1.2 ^d	Newborns (268)	NA	NA	NA	NA	NA	↓	Wu et al. 2017

^aNHANES participants.^bProspective study; genotoxicity assessed in adults and evaluated against PbB obtained during childhood (birth–78 months).^cUmbilical cord PbB.^dMaternal RBC lead at gestation week 28.

↑ = increase observed for specific effect; ↓ = decrease observed for specific effect; ↑↓ = decreased DNA methylations at some differentially methylated regions, and increased DNA methylation at other regions; 0 = no effect observed; DNA = deoxyribonucleic acid; MN = micronuclei; NA = not assessed; NHANES = National Health and Nutrition Examination Survey; RBC = red blood cell; SCE = sister chromatid exchange

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not find DNA damage in rats that received oral doses of lead nitrate at levels that produced necrotic changes in the liver. Global hypomethylation in hepatic DNA of rats was observed following single intravenous injection of Pb nitrate; hypomethylation was associated with an increase in cell proliferation. Exposure to Pb compounds is correlated with increased DNA synthesis and cell proliferation in the mammalian liver following intravenous injection. Numerous studies have assessed Pb compounds for chromosomal damage. Chromosomal aberrations were observed in bone marrow cells and spermatocytes of mice and rats following single or repeated exposure (intraperitoneal, gavage, dietary); however, the increase in aberrations did not consistently demonstrate dose-dependence.

Exposure to Pb compounds has been associated with SCEs in bone marrow of mice and rats following intravenous exposure. Studies assessing Pb compounds for MN formation in bone marrow erythrocytes of rats and mice were positive for multiple exposure routes (gavage, drinking water, intraperitoneal).

In vitro studies in human cell lines. *In vitro* studies in human cells lines have yielded mixed results. Pb acetate was weakly mutagenic in keratinocytes in the presence of 6-thioguanine, but not mutagenic in human foreskin, fibroblasts, or lung carcinoma cells. Results of assays assessing Pb compounds for DNA damage in human cell cultures were inconsistent. Double or single DNA strand breaks have been observed in peripheral blood lymphocytes, endothelial cells, hTERT-immortalized human skin fibroblasts, and HepG2 cells, but not in HeLa cells. DNA-protein crosslinks were observed in lymphoma cells exposed to 100 μ M Pb acetate, although cross-links were not observed for Pb nitrate at concentrations up to 10,000 μ M. Studies investigating SCEs and MN formation in human lymphocytes were positive following exposure to Pb nitrate and Pb chloride; however, no SCEs were observed in human lung cells or primary lymphocytes exposed to Pb. Interpretation of *in vitro* studies is challenging because concentrations used in these studies typically are very high and are not relevant to environmental or occupational exposures. As discussed in Section 3.1.2 (Toxicokinetics, Distribution), >99% of Pb in blood is bound to erythrocytes, leaving <1% available in plasma. Thus, plasma levels of Pb are far lower (at least two orders of magnitude) than the concentrations examined in *in vitro* studies in human cell lines. This leads to the introduction of considerable bias when interpreting study results (Bannon and Williams 2017).

In vitro studies in prokaryotic and mammalian cells. Mutagenicity tests of Pb compounds in prokaryotic organisms have mostly yielded negative results. Studies assessed gene mutation and DNA damage in *Salmonella typhimurium*, *Escherichia coli*, and *Bacillus subtilis* and gene conversion and mitotic recombination in *Saccharomyces cerevisiae* in the presence or absence of metabolic activation. The only

Pb compound that yielded positive results for gene mutation in *S. typhimurium* and *E. coli* was Pb bromide. Results of *in vitro* studies in mammalian cells for Pb compounds are mixed. Mutagenicity assays (hypoxanthine phosphorybosyl transferase [HPRT] and glutamate pyruvate transaminase [gpt] assays) were mutagenic in Chinese hamster ovary (CHO) and CHV79 cells at higher concentrations (>100 μ M) and negative at lower concentrations (<100 μ M). Pb chloride was the only Pb compound that was consistently mutagenic (gpt assay) in CHO cells at low concentrations (0.1–1.1 μ M; equivalent to 2.3–23 μ g/dL). Comet assays assessing Pb acetate for DNA damage (single strand breaks) in undifferentiated PC12 cells and mouse bone marrow mesenchymal stem cells were positive. Concentration-dependent increases in DNA-protein crosslinks were observed in hepatoma cells exposed to Pb nitrate, although Pb acetate did not induce single or double DNA strand breaks or DNA crosslinks in CHV79 cells. Exposure to Pb nitrate or Pb glutamate did not induce chromosomal aberrations in CHO cells. Assays assessing Pb compounds for SCEs in CHV79 cells were negative when fewer cells per concentration were utilized (25–30 cells), but were positive when the number of cells per concentration was increased (100 cells). Conflicting results were reported for MN formation in Chinese hamster cells.

Mechanisms of Action. Several mechanisms of action are likely involved in the genotoxic effects of Pb (EPA 2014c; IARC 2006; NTP 2016). Studies in occupationally exposed populations have found significant correlations between DNA breaks, decreased glutathione levels in the lymphocytes, and increased production of ROS, which may indicate oxidative stress as a possible mechanism for this response. The production of ROS after Pb exposure is a multi-pathway process, which results from oxidation of ALA, membrane and lipid oxidation, NAD(P)H oxidase activation, and antioxidant enzyme depletion. Disruption of functional metal ions that form enzymes (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx]) may occur as part of this process.

2.21 GENERAL CELLULAR MECHANISMS OF ACTION

2.21.1 Perturbation of Ion Homeostasis

Pb exerts many of its adverse effects by perturbing ion homeostasis. This perturbation occurs when Pb displaces other metal ions such as iron, calcium, zinc, magnesium, selenium, and manganese, interfering with the critical biological processes mediated by the ions themselves or by enzymes and proteins that require these ions (reviewed by EPA 2014c; Flora et al. 2012). Among the biological processes that Pb has been shown to affect via its impact on ion homeostasis are: calcium homeostasis; transportation of

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ions across cell membranes; cellular energetics; and the functioning of numerous proteins involved in cell signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways.

Calcium Homeostasis. Many of Pb's adverse effects can be traced back to its ability to displace calcium, leading to perturbations of numerous calcium-dependent cellular functions, including energy metabolism, apoptosis, cellular motility, signal transduction, and hormonal regulation (reviewed by EPA 2014c). In addition, intracellular migration of Pb has been shown in several cell lines (HEK293, HeLa, and PC12) to occur via calcium channels; higher Pb permeation correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.

Ion Transport. Pb has been shown to disrupt the transportation of critical cations across the cell membrane by decreasing the activity of ATPases (including Na⁺/K⁺-, Ca²⁺, and Mg²⁺-ATPases; reviewed by EPA 2014c). Pb-induced inhibition of ATPase activities has been shown in the kidneys, livers, erythrocytes, and brain synaptosomes of rats exposed to Pb in drinking water; in testes of rat pups exposed during lactation and postweaning; in primary cerebellar granule neuronal cultures of rat pups exposed pre- and postnatally; in rabbit kidney membranes and sarcoplasmic reticulum exposed *in vitro*; and in human erythrocyte ghosts. Furthermore, blood or hair Pb levels were inversely correlated with ATPase activities in erythrocytes in several human epidemiological studies.

In addition to ATPases, Pb's action on ion transport includes competitive inhibition of voltage-gated calcium channels (reviewed by EPA 2014c). A number of *in vitro* studies have demonstrated inhibition of calcium transport via voltage gated channels in cultured neurons and neuroblastoma cells, bovine adrenal chromaffin cells, and human embryonic kidney cells. Inhibition of calcium transportation via voltage-gated channels can disrupt release of neurotransmitters, and impaired neurotransmitter release has, in fact, been shown with Pb exposure at low *in vitro* levels. In addition to inhibiting calcium-dependent neurotransmitter release, Pb may mimic calcium, thereby increasing neurotransmitter release in some circumstances. For example, Pb exposure *in vitro* has been shown to induce the spontaneous release of norepinephrine from bovine adrenal chromaffin cells and increase the release of catecholamine from PC12 cells. It has been suggested that Pb may trigger spontaneous neurotransmitter release via activation of calcium/calmodulin-dependent protein kinase II-dependent phosphorylation of synapsin I, or by directly activating synaptotagmin I (a calcium-sensing protein that regulates neurotransmitter release). Intracellular migration of Pb has been shown to occur via calcium channels; higher Pb permeation in several cell lines (HEK293, HeLa, and PC12) correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.

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Pb also disrupts the activity of calcium-dependent potassium channels, as shown by increased efflux of potassium from inverted erythrocyte vesicles, and alterations in potassium channel activation in erythrocytes exposed to Pb (reviewed by EPA 2014c). The nature of the effect on potassium channels is dose-dependent; at low Pb concentrations (<10 μ M), potassium channels are activated, while inhibition of the channels is seen at higher Pb concentrations. As with calcium channels, alterations in potassium channel activity may also disrupt neurotransmitter release. In rats exposed to Pb *in utero* and postnatally, potassium-stimulated release of hippocampal GABA was decreased at low exposure levels, but enhanced GABA release was observed at higher exposures (in the absence of calcium).

Cellular Energetics. Evidence indicating that Pb exposure perturbs mitochondrial function and cellular energy metabolism is abundant (as reviewed by EPA 2014c). In rats exposed to Pb via diet or drinking water, renal tubular and epididymal mitochondria exhibited swelling, rupture of the outer membrane, distorted cristae or loss of cristae, vacuolization, inclusion bodies, and fusion with nearby mitochondria. As discussed further in Section 2.21.6, Apoptosis, Pb exposure has been shown to open the mitochondrial transmembrane pore, initiating the apoptotic caspase cascade. Evidence for Pb's effect on energy metabolism includes decreased ATP levels and/or adenylate energy charge (AEC) (along with increased ADP, AMP, and/or adenosine levels) in forebrain synaptosomes from rats exposed via drinking water, in cerebellar granule neuronal cultures from rats exposed by drinking water, in PC-12 cells exposed *in vitro*, and in isolated mitochondria exposed *in vitro*. In osteoblasts exposed *in vitro*, Pb inhibited both coupled and uncoupled respiratory oxygen use in mitochondria. Pb has been proposed to behave as a classic chemical uncoupler of respiration, abolishing the proton gradient necessary for oxidative phosphorylation. In the muscles of rats exposed to Pb in drinking water, decreased activities of the enzymes of complex I and IV of the respiratory chain were observed. However, in forebrain synaptosomes from rats exposed to Pb *in vivo*, oxidative phosphorylation was not inhibited, despite the fact that ATP levels were decreased.

Pb may affect cellular energetics via perturbation of the glycolysis pathway. Decreased glycolysis was observed in osteoblasts and erythrocytes exposed to Pb *in vitro* (reviewed by EPA 2014c). However, increased levels of glycolytic enzymes were noted in workers with higher blood Pb levels, when compared with workers with lower blood Pb, suggesting that Pb may activate anaerobic glycolysis.

Depletion of cellular nucleotide pools required for ATP synthesis has also been observed after Pb exposure of human erythrocytes *in vitro* and in rats exposed via drinking water (reviewed by EPA 2014c). This effect may be mediated by Pb-induced inhibition of enzymes involved in nucleotide biosynthesis in

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erythrocytes, including adenine phosphoribosyltransferase (see Impaired Protein Function below) and NAD synthetase (which depends on magnesium for activity). In support of the latter mechanism, in humans exposed to Pb, PbB levels were inversely correlated with NAD synthetase activity.

Impaired Protein Function. Pb impairs the functions of numerous proteins, with concomitant effects on signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways. The mechanisms by which Pb alters protein activity are by displacing metal cofactors or binding to sulfhydryl groups (reviewed by EPA 2014c). Table 2-49 shows proteins known to be bound to or otherwise altered by Pb, along with their functions and brief summaries of the evidence for Pb-induced alterations. As the table suggests, Pb-induced alterations in proteins may play a role in its adverse effects on the neurological, hematological, cardiovascular, and skeletal systems.

Through its displacement of calcium, Pb perturbs the function of several calcium-dependent proteins, including protein kinase C, calmodulin, osteocalcin, the mitochondrial transmembrane pore, and NAD(P)H oxidase (reviewed by EPA 2014c). The protein kinase C family of enzymes is important to cell signaling, growth, and differentiation. Pb exposure has been shown to activate PKC in a number of cell types tested *in vitro* (see table), and to decrease its activity in mouse macrophages and rat brain cortex. Pb stimulates calmodulin activity, as shown by increased activity of several calmodulin-dependent enzymes, and increased binding of calmodulin to brain membranes. In experiments testing the affinity of metal cations to bind calmodulin, Pb was more potent than mercury, cadmium, iron, and even calcium. Pb binding to calmodulin has been postulated as a mechanism for its stimulatory effect on Ca²⁺/Mg²⁺ ATPase. Calmodulin plays an essential role in maintaining calcium homeostasis and regulating calcium-dependent cell signaling important to structural integrity, gene expression, and maintaining membrane potential (reviewed by EPA 2014c).

Skeletal effects of Pb may be mediated in part by Pb's interference with another calcium-dependent protein: osteocalcin (reviewed by EPA 2014c). The binding of Pb to osteocalcin is much stronger than binding of calcium, and Pb binding alters the structure of osteocalcin. The conformational change in osteocalcin induced by Pb has been postulated as the mechanism by which Pb exposure diminishes the adsorption of osteocalcin to hydroxyapatite.

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Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Calcium-dependent proteins		
Calcium binding proteins (CABPs I and II)	Regulation of calcium signaling, especially in neuronal cells	No data -Ca ²⁺ displacement shown <i>in vitro</i> .
Ca ²⁺ -dependent K ⁺ channel	Ion transport; activation of channels regulates neuron firing and neurotransmitter release	Activates or inhibits channel -Pb promoted efflux of K ⁺ from inverted red blood cell vesicles. -Pb induced activation of K ⁺ channel in erythrocytes at low Pb concentrations and inhibited activity at high concentrations.
Calmodulin	Cell signaling, including structural integrity, gene expression, and maintenance of membrane potential	Amplifies calmodulin activity -Pb activated calmodulin-dependent phosphodiesterase and cyclic nucleotide phosphodiesterase activities. -Pb stimulated brain membrane phosphorylation. -Pb increased binding of calmodulin to brain membranes.
Mitochondrial transmembrane pore (MTMP)	Triggers mitochondrial apoptosis cascade when open	Opens MTMP, triggering apoptosis -Pb increased mitochondria-regulated apoptotic indicators (cytochrome c, caspases) in rat retinal rod cells and hepatic oval cells <i>in vitro</i> .
NAD(P)H oxidase	Inflammatory mediator; triggers oxidative burst (via production of superoxide) in response to infection	Increases activity, leading to ROS generation -Pb increased protein levels of glycosylated subunit of NAD(P)H oxidase in brain, heart, and renal cortex of rats exposed via drinking water and in human coronary artery endothelial cells <i>in vitro</i> .
Osteocalcin	Bone resorption, osteoclast differentiation, and bone growth	Alters binding of osteocalcin to hydroxyapatite -Pb exposure has been shown to both increase and decrease binding of osteocalcin to hydroxyapatite.
Parvalbumin	Unclear; may buffer Ca ²⁺ levels; expressed at high levels in interneurons	No data -Ca ²⁺ displacement shown <i>in vitro</i> .
Phospholipase A ₂	Hydrolyze fatty acids from membrane phospholipids; released fatty acids are metabolized to bioactive lipid mediators	No data -Ca ²⁺ displacement shown <i>in vitro</i> .

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Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Protein kinase C (PKC)	Cell signaling, especially growth and differentiation	Increases or decreases activity -Pb shown to activate PKC <i>in vitro</i> in bovine adrenal chromaffin cells, rat brain microvessels, human erythrocytes, and rabbit mesenteric arteries. -Pb decreased PKC activity in mouse macrophages and rat brain cortex.
Synaptotagmin I	Ca ²⁺ sensor regulating neurotransmitter release	No data -Ca ²⁺ displacement shown <i>in vitro</i> .
Troponin C	Ca ²⁺ sensor regulating muscle contraction	No data -Ca ²⁺ displacement shown <i>in vitro</i> .
Heme-dependent proteins		
Catalase	Antioxidant; scavenger of hydrogen peroxide	Increases or decreases activity -Pb shown to increase activity in some studies and decrease activity in others, possibly due to differences in species, exposure duration, dose, or other study design variations.
Guanylate cyclase	Catalyzes synthesis of cGMP, which stimulates vasorelaxation in vascular tissues	Impairs production of cGMP -Pb reduced cGMP in plasma and urine of rats exposed by drinking water. -Pb decreased protein levels of soluble guanylate cyclase in vascular tissue.
Hemoglobin	Oxygen transportation	Impairs heme production needed for synthesis of hemoglobin -Pb binding to hemoglobin demonstrated in human blood.
Magnesium-dependent proteins		
Adenine and hypoxanthine/guanine phosphoribosyltransferases	Recycling of nucleotides	Inhibits activity -Pb inhibited phosphoribosyltransferase activities in erythrocytes of rats exposed via drinking water and in human erythrocytes <i>in vitro</i> .
NAD synthetase (Mg)	Nucleotide biosynthesis	Decreases activity -Blood Pb was inversely correlated with NAD synthetase activity in humans.
Pyrimidine 5'-nucleotidase	Dephosphorylates pyrimidine nucleotides in erythrocytes, preserving purine nucleotides (e.g., ATP, ADP) necessary for energy	Alters protein conformation and amino acid positioning at active site, possibly by occupying active site -Pb binding and protein conformation changes observed <i>in vitro</i> . -Pyrimidine nucleotide accumulation in erythrocytes is seen in Pb poisoning.

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Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Zinc-dependent proteins		
δ -ALA (δ -ALAD or porphobilinogen synthase)	Heme biosynthesis (converts δ -ALA to porphobilinogen)	Depletes δ -ALAD, preventing heme biosynthesis and leading to accumulation of δ -ALA. - δ -ALAD shown to be major binding target of Pb in erythrocytes.
GATA zinc finger proteins	Activation/suppression of DNA transcription	Decreases ability of GATA proteins to bind to DNA and regulate transcription -Pb binding to cysteine residues and displacement of Zn from GATA proteins observed <i>in vitro</i> . -Pb-bound GATA proteins exhibited reduced DNA binding.
Transcription factors TFIIIA, Sp1, and Erg-1	Activation/suppression of DNA transcription	Decreases ability of TFIIIA, Sp1, and Erg-1 to bind to DNA and regulate transcription -Pb exposure caused dissociation of TFIIIA-DNA adducts. -Pb exposure altered DNA binding profile of Sp-1 and Erg-1 in rat pups exposed via lactation, leading to changes in gene expression.
Proteins altered by lead interaction with other cations or sulphydryl groups		
ATPases (Ca^{2+} -, Mg^{2+} -, and Na^+/K^+ -)	Ion transport	Decreases activity -Pb decreased ATPase activities in brain, kidneys, liver, testes, and erythrocytes (cells or tissues).
cGMP phosphodiesterase (Zn, Mg)	Hydrolysis of cGMP	Inhibits activity -Decreased activity observed in homogenized bovine retinas exposed to Pb <i>in vitro</i> .
Ferrochelatase (Fe)	Heme biosynthesis; incorporates Fe^{2+} into protoporphyrin IX to form heme	Inhibits insertion of Fe into protoporphyrin ring, leading to substitution by Zn -Zn-protoporphyrin levels correlated with blood Pb levels in humans.
Glutathione peroxidase and glutathione S-transferase (Se)	Antioxidants	Reduces uptake of Se and depletes cellular GSH and protein thiols, resulting in altered GST and GPx enzyme activities -Decreased activity, often with compensatory upregulation of the enzymes, seen in Pb-exposed animals and humans.

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Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Metallothionein (Zn, Cu)	Trace element homeostasis; free radical scavenging	Sequestered by metallothionein, providing protective effect -Pb toxicity is seen at lower blood Pb levels in humans with low expression of metallothionein or low Pb binding to metallothionein. -Pb induced production of metallothionein in mice exposed via intraperitoneal or intravenous injection and in rats exposed via intraperitoneal injection, but not in rats exposed via drinking water. -Presence of zinc metallothionein reduced effect of Pb on membrane integrity in hepatocytes exposed <i>in vitro</i> . -Pb nephrotoxicity and preneoplastic and neoplastic lesions in the testes, bladder, and kidneys were more severe or seen at increased incidences in metallothionein-null mice compared with wild-type.
Superoxide dismutase	Antioxidant; catalyzes conversion of superoxide to hydrogen peroxide; inhibits oxidative inactivation of nitric oxide	Increased or decreased activity -Pb shown to increase activity in several studies and decrease activity in others, possibly due to differences in species, exposure duration, dose, or other study design variations.
Thymosin β -4	Actin regulation; exerts angiogenic, anti-inflammatory, and cardioprotective effects on the heart	No data -Pb binding observed <i>in vitro</i> .

ADP = adenosine diphosphate; δ -ALA = aminolevulinic acid; δ -ALAD = aminolevulinic acid dehydratase; ATP = adenosine triphosphate; ATPase = family of phosphatase enzymes that breakdown ATP and ADP; cGMP = cyclic guanosine monophosphate; DNA = deoxyribonucleic acid; Erg-1 = early growth response protein 1; GST = glutathione S-transferase; GSH = glutathione; GPx = glutathione peroxidase; NAD = nicotinamide adenine dinucleotide; NAD(P)H = the reduced form of nicotinamide adenine dinucleotide phosphate; ROS = reactive oxygen species; Sp1 = Transcription factor specificity protein 1; TFIIIA = transcription factor IIIA

Sources: EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012; Gonick 2011

Other calcium-dependent proteins bound to or impaired by Pb include parvalbumin, phospholipase A2, synaptotagmin I (see *Ion Transport* above), troponin C, the mitochondrial transmembrane pore (see Section 2.21.6, Apoptosis), and NAD(P)H oxidase (see Section 2.21.3, Oxidative Stress) (reviewed by EPA 2014c).

Pb also displaces zinc in a number of critical proteins, including ALAD, GATA proteins, and several zinc-binding transcription factors (TFIIIA, Sp1, and Erg-1) (reviewed by EPA 2014c). Section 2.8 provides a detailed discussion of Pb's effects on ALAD and heme biosynthesis. Binding of Pb to zinc-binding domains in GATA proteins and transcription factors inhibits their binding to DNA and impairs their ability to regulate gene expression (see Section 2.21.5, *Epigenetic Effects*, below for further detail).

Through competitive inhibition of magnesium-dependent proteins, Pb also affects the activities of adenine and hypoxanthine/guanine phosphoribosyltransferases, cyclic guanosine monophosphate (cGMP) phosphodiesterase, and pyrimidine 5'-nucleotidase (reviewed by EPA 2014c). In erythrocytes, adenine phosphoribosyltransferase catalyzes the synthesis of nucleotides via the adenine salvage pathway; Pb exposure has been shown to decrease nucleotide pools in human erythrocytes *in vitro* and in erythrocytes from rats exposed via drinking water. Inhibition of cGMP phosphodiesterase, a magnesium-dependent enzyme regulating cGMP signaling in smooth muscle contraction and relaxation, has been observed in homogenized bovine retinas cultured with Pb. Pb inhibits magnesium binding in pyrimidine 5'-nucleotidase, inhibiting its activity by changing its active site conformation. Pyrimidine 5'-nucleotidase occurs at high levels in erythrocytes, where it dephosphorylates pyrimidine nucleotides while leaving purine nucleotides (used as an energy source in erythrocytes, as they lack mitochondria), intact. Basophilic stippling of erythrocytes, a common feature of Pb poisoning, is also seen in individuals with inherited pyrimidine-5'-nucleotidase deficiency (Rees et al. 2003), providing supporting evidence that Pb inactivates the enzyme.

2.21.2 Protein Binding/Sequestration

A number of low molecular-weight proteins, including metallothionein, have been shown to bind (through thiol residues) to Pb, forming inclusion bodies in the kidney, liver, lung, and glial cells (reviewed by EPA 2014c; Gonick 2011). In the case of metallothionein, the effect of the binding is to sequester Pb, protecting the exposed cells and tissues. The strongest evidence for the protective effect of metallothionein comes from studies of metallothionein-null mice, which exhibit more severe Pb-induced renal toxicity, as well as increased incidences of neoplastic and nonneoplastic lesions in the testes,

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bladder, and kidneys, compared with wild-type mice. Supporting this finding is the observation that higher blood Pb levels, as well as more pronounced Pb-induced effects on systolic blood pressure and kidney function, were observed in exposed workers with a metallothionein mutation (compared with those exhibiting a normal metallothionein genotype). Metallothionein levels have been shown to be induced by Pb exposure in mice and in rats pretreated with zinc.

In erythrocytes, the major Pb-binding protein is ALAD; hemoglobin also binds Pb (reviewed by EPA 2014c; Gonick 2011). In exposed humans, polymorphisms in the ALAD gene that increase the Pb-binding capacity of its protein product (e.g., ALAD-2) were observed to decrease blood Pb levels and biomarkers for Pb toxicity, including plasma levulinic acid, zinc protoporphyrin, cortical bone Pb levels, and dimercaptosuccinic acid-chelatable Pb levels. Other proteins that bind Pb in erythrocytes include pyrimidine 5'-nucleotidase and acyl-coenzyme A binding protein.

In rat kidneys, inclusion bodies consisting of Pb-bound proteins have been observed in a number of studies (reviewed by EPA 2014c; Gonick 2011). These inclusion bodies are initially observed in the cytosol, but appear to translocate to the nucleus, as they disappear concomitantly with the appearance of intranuclear inclusion bodies. The primary Pb-bound protein in the kidney (a 32 kDa protein with an isoelectric point of 6.3, named p32/6.3) has not been identified, but has been shown to be enriched in the brain and is highly conserved across species (rats, mice, dogs, chickens, and humans). Studies in rats exposed by food or drinking water showed that p32/6.3 is not found in the kidneys of untreated rats but rather is induced by Pb exposure. Other Pb-binding proteins identified in the kidneys of rats or humans include acyl-CoA binding protein and thymosin β -4 (the latter is involved in actin regulation).

2.21.3 Oxidative Stress

Pb exposure has resulted in oxidative damage in several tissues in humans and rats, including the brain, kidneys, reproductive organs, heart, and erythrocytes (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). Oxidative damage may play a role in Pb-induced toxicity in these tissues, including neurological effects, hypertension and other cardiovascular effects, and diminished fertility. Pb induces oxidative stress through several mechanisms, including increased production of ROS via inhibition of heme biosynthesis and activation of NAD(P)H oxidase; stimulation of lipid peroxidation and alteration of lipids enhancing their susceptibility to lipid peroxidation; and inactivation and/or depletion of antioxidant enzymes. Through the increased production of ROS, which sequesters nitric oxide, Pb exposure also leads to perturbation of nitric oxide signaling that is critical to vasodilation.

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Exposure to Pb triggers increased production of ROS via its effects on heme biosynthesis. In erythrocytes, Pb has been shown to bind to δ -ALAD as well as to inhibit its activity by interfering with the zinc ions the enzyme requires for heme biosynthesis; in fact, inhibition of δ -ALAD activity is inversely correlated with PbB levels in humans (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). δ -ALAD catalyzes the conversion of δ -ALA to porphobilinogen; thus, its inhibition results in accumulation of δ -ALA in blood and in urine. In these environments, δ -ALA undergoes autoxidation, yielding superoxide and hydroxyl radicals, as well as hydrogen peroxide and an ALA radical. In addition, through subsequent reduction of ferricytochrome c and transfer of electrons from oxyhemoglobin, methemoglobin, and ferric and ferrous iron complexes, oxidized δ -ALA also produces ROS.

Pb may also increase intracellular ROS by upregulating expression of NAD(P)H oxidase, an enzyme that produces superoxide anion via reaction of NAD(P)H and molecular oxygen, but data are limited (reviewed by EPA 2014c). Increased protein expression of the glycosylated subunit of NAD(P)H oxidase was observed in tissues of rats exposed to Pb in drinking water, and in human endothelial cells *in vitro*.

ROS produced via Pb effects on δ -ALA and/or NAD(P)H oxidase can damage membrane lipids through peroxidation. In addition, however, Pb has been shown to catalyze ferrous ion-initiated lipid peroxidation (reviewed by EPA 2014c). Furthermore, there is evidence that Pb exerts effects on membrane lipids that render them more vulnerable to peroxidation (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). For example, Pb has been shown to alter the composition of fatty acids in chicks exposed by drinking water, such that a higher fraction of longer fatty acids (such as arachidonic acid) and lower fraction of shorter fatty acids (compared with controls) were observed. Oxidative potential of fatty acids is correlated with both length and desaturation (i.e., the number of double bonds; the hydrogen on a double bond is easier to remove). It has been proposed that Pb may stimulate both elongation and desaturation of fatty acids, increasing their susceptibility to peroxidation. Alterations in lipid composition may also affect membrane permeability and functions, including the activity of membrane-associated enzymes, solute transport functions, endo- and exocytosis, and signal transduction.

Increased circulating ROS (specifically, superoxide anion) can inactivate nitric oxide, an endogenously produced molecule that plays an important role in vasodilation (reviewed by EPA 2014c). Depletion of nitric oxide has been observed in animals exposed to Pb, as well as in human and animal immune cells treated *in vitro*. In addition, nitric oxide depletion is believed to be the mechanism behind Pb-induced upregulation of nitric oxide synthases seen in vascular tissues after Pb exposure. Nitric oxide depletion

2. HEALTH EFFECTS

occurs when it reacts with superoxide anion to form the highly reactive peroxynitrite anion, which itself damages DNA and proteins. Levels of nitrotyrosine, which results from peroxynitrite-induced nitration of tyrosine residues in proteins, were increased in plasma and other tissues after *in vivo* exposure to Pb. In vascular tissues, nitric oxide induces vasorelaxation via cGMP signaling (reviewed by EPA 2014c). Exposure of rats to Pb in drinking water for 1–3 months markedly reduced cGMP levels in both blood and urine. Synthesis of cGMP is catalyzed by soluble guanylate cyclase, a heme-dependent enzyme. Pb exposure has been shown to reduce protein levels of soluble guanylate cyclase in vascular tissues; alleviation of this effect by antioxidant treatment (ascorbic acid) demonstrated that this finding was mediated, at least in part, by increased oxidative stress.

In human epidemiological studies, the ratio of oxidized glutathione (glutathione disulfide or GSSG) to reduced glutathione (GSH), a measure of oxidative stress, was positively correlated with blood Pb levels (reviewed by EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012). The effects of Pb on oxidative stress levels may occur through depletion of antioxidant levels in addition to stimulation of ROS, as oxidative stress occurs when the antioxidant capacity of the body is exceeded. Pb forms covalent bonds with sulfhydryl groups in antioxidant enzymes such as GSH, glutathione reductase (GR), and glutathione S-transferase (GST) (reviewed by EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012). In humans, animals, and *in vitro* studies, decreased GSH in blood and organs has been associated with Pb exposure. After long-term exposure to Pb, increased GSH levels, attributed to compensatory upregulation of GSH biosynthesis, have been reported. Like GSH, GR (which reduces GSSG back to GSH) and GST also have disulfides at their active site that could be bound by Pb. Studies examining GR and GST activity after Pb exposure used varying study designs and showed both increases and decreases; it is not clear whether the differences in results reflect species, strain, dose, or duration differences.

Pb's capacity to compete with cations and its interference with heme biosynthesis have also been suggested as potential mechanisms for its ability to alter levels of SOD, CAT, GPx, and GST (reviewed by EPA 2014c; Flora et al. 2012; Ahamed and Siddiqui 2007). SOD forms require copper, zinc, or manganese, cations that Pb may displace, while catalase is a heme-dependent enzyme. Several studies in humans and animals have shown alterations in SOD and CAT activity, with some evidence for a nonlinear dose-response relationship. EPA (2014c) suggested that increased SOD and CAT may occur at low doses as a result of ROS generation by Pb, while at higher doses, Pb may inactivate the enzymes. Pb exposure also alters activities of GPx and GST, potentially by reducing the uptake of selenium (required by GPx) and/or disrupting protein thiols (necessary for GST function). Decreased GPx and GST

activities have been observed, along with compensatory upregulation of these enzymes, in Pb-exposed humans and animals.

2.21.4 Inflammation

Increasing oxidative stress through ROS generation and depletion of antioxidant enzymes may be one mechanism by which Pb induces an inflammatory response (reviewed by EPA 2014c). Inflammation, considered a hallmark of Pb exposure (EPA 2014c), may also be triggered by pro-inflammatory signaling and cytokine production. Inflammation has been seen after Pb exposure in many different cell types, as well as in the kidneys of rats exposed to Pb in drinking water.

Oxidative stress is known to activate the pro-inflammatory nuclear transcription factor kappa B (NFκB). In the rat kidney, Pb-induced inflammation was accompanied by activation of NFκB as well as lymphocyte and macrophage infiltration (reviewed by EPA 2014c). Pb has been shown to stimulate the expression of pro-inflammatory signal mediators including NFκB, activator protein-1 (AP-1), and c-Jun, and to stimulate phosphorylation of the Erk/MAPK pathway. In addition, exposure to Pb is associated with increased production of prostaglandins, which also mediate pro-inflammatory messaging. Increases in arachidonic acid production, leading to increases in prostaglandins E2 and F2 and thromboxane levels, have been seen in Pb-exposed workers as well as in animals and in cultured cells systems exposed to Pb. In vascular smooth muscle cells, Pb has been shown to activate phospholipase A2, which may explain its ability to stimulate the release of arachidonic acid.

In both human epidemiological and laboratory animal studies, Pb exposure has been demonstrated to increase cytokine production (reviewed by EPA 2014c). In these studies, a fairly consistent picture of decreasing Th-1 cytokines and increasing Th-2 cytokines has emerged. EPA (2014c) outlined three modes by which Pb influences cytokine production: (1) direct action on macrophages to increase pro-inflammatory cytokines such as TNF-α and interleukin 6 (IL-6); (2) skew the ratio of IL-12 to IL-10, leading to suppression of Th-1 cell responses and stimulation of Th-2 cell responses; and (3) during acquired immune response occurring after Pb exposure, production of cytokines by Th-1 lymphocytes is suppressed, and Th-2 cytokines are increased. The net result of these changes is consistent with the pro-inflammatory picture seen with Pb exposure.

Human epidemiological studies have provided evidence that Pb exposure skews immune responses toward Th-2 pro-inflammatory responses (reviewed by EPA 2014c). Higher blood Pb levels in children

2. HEALTH EFFECTS

were associated with increased serum levels of IL-4 (which induces differentiation of Th0 cells to the Th-2 phenotype) and lower levels of interferon gamma (IFN- γ). In adult students in Korea, higher blood Pb levels were positively associated with increased TNF- α and IL-6; a 1 $\mu\text{g/dL}$ increase in blood Pb was associated with a 23% increase in log TNF- α and a 26% increase in IL-6. Finally, in occupationally-exposed workers, higher blood Pb levels were associated with increases in IL-2, IL-10, IL-6, TNF- α , and granulocyte colony stimulating factor (G-CSF), and, in one study, lower levels of Th-1 cytokines IL-1 β and IFN- γ . Similar effects were seen in mice exposed to Pb in feed; blood levels of Th-1 cytokines (IL-2 and IFN- γ) were decreased at low dietary doses, while increases in IL-4 were seen as the Pb dose increased. Based on these data, EPA (2014c) suggested that the immune system response to Pb may exhibit nonlinearities at low doses. In rats exposed to Pb via intraperitoneal injection, increased levels of TNF- α were seen in the hippocampus, and increased IL-6 was noted in the forebrain. *In vitro* data have also shown alterations in cytokine production after exposure to Pb.

2.21.5 Epigenetic Effects

In a small number of studies, Pb has been shown to induce epigenetic effects, including perturbations in DNA methylation as well as alterations in mitogenesis (reviewed by EPA 2014c; Bakulski et al. 2012). In human studies, maternal blood Pb was correlated with decreased DNA methylation of Alu retrotransposable elements in umbilical cord blood, and bone Pb levels were correlated with decreased DNA methylation of LINE-1 retrotransposons in elderly men, while higher blood Pb was associated with increased methylation of p16 tumor suppressor gene promoters in occupationally exposed individuals. Other evidence for effects of Pb on DNA methylation include a study in primates in which the activity of DNA methyltransferase 1 was decreased by early life Pb exposure, and *in vitro* data showing decreased global DNA methylation in rat pheochromocytoma cells. Hypomethylation of DNA has been shown to trigger changes in gene expression that may lead to alterations in tissue differentiation.

Pb exposure also induces effects on mitogenesis, including both increases in cell proliferation and decreases in some systems (reviewed by EPA 2014c). Increased cell proliferation and/or DNA synthesis have been reported in workers exposed to Pb, in hepatocytes of rats exposed by intravenous injection of Pb nitrate, and in mouse lung after exposure to Pb acetate via inhalation. In *in vitro* studies, results were mixed: in some cases cell proliferation was decreased, as Pb exposure resulted in cell cycle arrest. Effects of Pb exposure on gene expression have been demonstrated in several studies (reviewed by EPA 2014c). Although the exact mechanisms by which Pb alters gene expression have not been elucidated, Pb is known to interfere with GATA proteins and several transcription factors (TFIIIA, Sp1, and Erg-1)

through its interaction with zinc-binding domains, reducing the ability of these proteins to bind to DNA and exert their transcriptional regulation functions. *In vivo* and *in vitro* studies have shown that Pb alters the transcription of genes for metabolic enzymes including GST-P and GST-Ya, CYPs 1A1 and 1A2, and NAD(P)H:quinone oxidoreductase, as well as genes involved in the pentose phosphate pathway and amino acid metabolism.

2.21.6 Apoptosis

As discussed earlier, Pb is capable of opening the mitochondrial transmembrane pore (MTMP, the first step in the mitochondrial apoptosis cascade), possibly by displacing calcium on the matrix side of the pore (reviewed by EPA 2014c). Evidence for this effect includes observations of mitochondrial swelling and decreased membrane potential in rat primary cerebellar granule neuronal cultures, astroglia, proximal tubule cells, and retinal rod photoreceptor cells. In addition, release of cytochrome c and activation of caspases 3 and 9 were observed in rat retinal rod cells and hepatic oval cells exposed to Pb *in vitro*. In lymphocytes of Pb-exposed humans, increased apoptosis, karyorrhexis, and karyolysis (early indicators of apoptosis) were observed. Other tissues have also exhibited increased apoptosis after Pb exposure, including liver, fibroblasts, and alveolar macrophages.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Overview. The toxicokinetics of Pb in humans has been extensively studied and several models have been published that simulate the absorption and complex distribution and elimination of Pb from blood, soft tissues, and bone.

- Absorption:
 - Respiratory tract: Inorganic Pb in submicron size particles can be almost completely absorbed through the respiratory tract, whereas larger particles may be moved after deposition in the respiratory tract by mucociliary clearance toward the oropharynx and swallowed.
 - Gastrointestinal tract: The fraction of ingested Pb absorbed from the gastrointestinal tract depends on many factors, including age, diet, nutrition, and physiological characteristics of Pb in the medium ingested.
 - Children can absorb 40–50% of an oral dose of water-soluble Pb compared to 3–10% for adults.
 - Gastrointestinal absorption of inorganic Pb occurs primarily in the duodenum by saturable mechanisms.
 - Dermal: Inorganic Pb can be absorbed following inhalation, oral, and dermal exposure, but the latter route is much less efficient than the former two, with the exception of hand-to-mouth behavior. Studies in animals have shown that organic Pb is absorbed through the skin.
- Distribution:
 - The distribution of Pb in the body is route-independent and, in adults, approximately 94% of the total body burden of Pb is in the bones compared to approximately 73% in children.
 - Pb in blood is primarily in red blood cells. Conditions such as pregnancy, lactation, menopause, and osteoporosis increase bone resorption and consequently also increase Pb in blood.

- Pb can be transferred from the mother to the fetus and also from the mother to infants via maternal milk.
- Metabolism:
 - Metabolism of inorganic Pb consists of formation of complexes with a variety of protein and nonprotein ligands.
 - Organic Pb compounds are actively metabolized in the liver by oxidative dealkylation by P-450 enzymes.
- Excretion:
 - Pb is excreted primarily in urine and feces regardless of the route of exposure. Minor routes of excretion include sweat, saliva, hair, nails, breast milk, and seminal fluid.
 - Elimination of Pb is multiphasic, reflecting pools of Pb in the body that have varying retention times. The apparent elimination half-time in blood varies with age and exposure history and ranges from 1 week to 2 years. Elimination of Pb from bone occurs with an apparent half-time of 1–2 decades.
- Toxicokinetics models:
 - Several models of Pb pharmacokinetics have been proposed to characterize such parameters as intercompartmental Pb exchange rates, retention of Pb in various tissues, and relative rates of distribution among the tissue groups.
 - Some models are currently being used or are being considered for broad application in Pb risk assessment.

3.1.1 Absorption

Inhalation Exposure

Inorganic Pb. Inorganic Pb in ambient air consists of aerosols of particulates that can be deposited in the respiratory tract when the aerosols are inhaled. Amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose versus mouth breathing), airway geometry, and air-stream velocity within the respiratory tract (James et al. 1994). Absorption of deposited Pb is influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles

(>2.5 μm) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the esophagus and swallowed. Smaller particles (2.5 to <1 μm), which can be deposited in the alveolar region, can be absorbed after extracellular dissolution or ingestion by phagocytic cells (Bailey and Roy 1994).

Deposition in, and clearance from, the respiratory tract have been measured in adult humans (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). In these studies, exposures were to Pb-bearing particles having mass median aerodynamic diameters (MMADs) below 1 μm and, therefore, deposition of the inhaled Pb particles can be assumed to have been primarily in the bronchiolar and alveolar regions of the respiratory tract (James et al. 1994) where transport of deposited Pb to the gastrointestinal tract is likely to have been only a minor component of particle clearance (Hursh et al. 1969). Approximately 25% of inhaled Pb chloride or Pb hydroxide (MMAD 0.26 and 0.24 μm , respectively) was deposited in the respiratory tract in adult subjects who inhaled an inorganic Pb aerosol through a standard respiratory mouthpiece for 5 minutes (Morrow et al. 1980). Approximately 95% of deposited inorganic Pb that was inhaled as submicron particles was absorbed (Hursh et al. 1969; Wells et al. 1975). Rates of clearance from the respiratory tract of inorganic Pb inhaled as submicron particles of Pb oxide, or Pb nitrate, were described with half-times ($t_{1/2}$) of 0.8 hours (22%), 2.5 hours (34%), 9 hours (33%), and 44 hours (12%) (Chamberlain et al. 1978). These rates are thought to represent, primarily, absorption from the bronchiolar and alveolar regions of the respiratory tract. Absorption half-times have been estimated in adults who inhaled aerosols of Pb and bismuth isotopes generated from decay of ^{220}Rn or ^{222}Rn (Butterweck et al. 2002; Marsh and Birchall 1999). The absorption half-time was approximately 10 hours in subjects who inhaled aerosols having an activity median particle diameter of approximately 160 nm (range 50–500 nm), and approximately 68 minutes for aerosols having diameters of approximately 0.3–3 nm.

Rates and amounts of absorption of inhaled Pb particles >2.5 μm will be determined, primarily by rates of transport to and absorption from the gastrointestinal tract. Absorption of Pb from the gastrointestinal tract varies with the chemical form ingested, age, meal status (e.g., fed versus fasted), and nutritional factors (see Section 3.1.1 *Oral Exposure*).

Organic Pb. Clinical studies of subjects who inhaled tetraethyl or tetramethyl Pb found that 60–80% of the Pb deposited in the respiratory tract was absorbed (Heard et al. 1979). Following a single exposure to vapors of radioactive (^{203}Pb) tetraethyl Pb (approximately 1 mg/m^3 breathed through a mouthpiece for 1–2 minutes) in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of

which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). One hour after the exposure, approximately 50% of the ^{203}Pb burden was associated with liver, 5% was associated with kidney, and the remaining burden was widely distributed throughout the body (determined by external gamma counting), suggesting near complete absorption of the Pb that was not exhaled. In a similar experiment conducted with (^{203}Pb) tetramethyl Pb, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. The distribution of ^{203}Pb 1 hour after the exposure was similar to that observed following exposure to tetraethyl Pb.

The relatively rapid and near complete absorption of tetraalkyl Pb that is inhaled and deposited in the respiratory tract is also supported by studies conducted in animal models (Boudene et al. 1977; Morgan and Holmes 1978).

Oral Exposure

Inorganic Pb. The extent and rate of gastrointestinal absorption of ingested inorganic Pb are influenced by physiology (e.g., age, fasting, nutritional calcium and iron status, pregnancy), physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, and Pb species) and the ingested Pb dose.

Mechanisms of Absorption. Gastrointestinal absorption of inorganic Pb occurs primarily in the duodenum (Mushak 1991). The exact mechanisms of absorption are unknown and may involve active transport and/or diffusion through intestinal epithelial cells (transcellular) or between cells (paracellular), and may involve ionized Pb (Pb^{+2}) and/or inorganic or organic complexes of Pb. *In vitro* studies of Pb speciation in simulated human intestinal chyme indicate that the concentration of ionized Pb is negligible at Pb concentrations below 10^{-3} M (207 mg/L) and that Pb phosphate and bile acid complexes are the dominant forms when inorganic Pb salts (e.g., Pb nitrate) are added to chyme (Oomen et al. 2003a). However, these complexes may be sufficiently labile to provide ionized Pb for transport across cell membranes (Oomen et al. 2003b). Saturable mechanisms of absorption have been inferred from measurements of net flux kinetics of Pb in *in situ* perfused mouse intestine, *in situ* ligated chicken intestine, and *in vitro* isolated segments of rat intestine (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981). By analogy to other divalent cations, saturable transport mechanisms for Pb^{+2} may exist within the mucosal and serosal membranes and within the intestinal epithelial cell. For calcium and iron, these are thought to represent membrane carriers (e.g., $\text{Ca}^{2+}\text{-Mg}^{2+}\text{-ATPase}$, $\text{Ca}^{2+}/\text{Na}^{+}$ exchange, DMT1) or facilitated diffusion pathways (e.g., Ca^{2+} channel) and

intracellular binding proteins for Ca^{2+} (Bronner et al. 1986; Fleming et al. 1998b; Gross and Kumar 1990; Teichmann and Stremmel 1990).

Effect of Age. Gastrointestinal absorption of water-soluble Pb appears to be higher in children than in adults. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate that approximately 40–50% of ingested Pb is absorbed (Alexander et al. 1974; Ziegler et al. 1978). In adults, estimates of absorption of ingested water-soluble Pb compounds (e.g., Pb chloride, Pb nitrate, Pb acetate) ranged from 3 to 10% in fed subjects (Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980; Watson et al. 1986). Data available on Pb absorption between childhood and adulthood ages are very limited. While no absorption studies have been conducted on subjects in this age range, the kinetics of the change in stable isotope signatures of blood Pb in mothers and their children, as both come into equilibrium with a novel environmental Pb isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested Pb (Gulson et al. 1997b).

Studies in experimental animals provide additional evidence for an age-dependency of gastrointestinal absorption of Pb. Absorption of Pb, administered as Pb acetate (6.37 mg Pb/kg, gavage), was higher in juvenile Rhesus monkeys (38% of dose) compared to adult female monkeys (26% of the dose) (Pounds et al. 1978). Rat pups absorb approximately 40–50 times more Pb from the diet than do adult rats (Aungst et al. 1981; Forbes and Reina 1972; Kostial et al. 1978). This age difference in absorption may be due, in part, to the shift from the neonatal to adult diet, and to postnatal physiological development (enzymes, transporters, gastric pH) of the gastrointestinal tract (Weis and LaVelle 1991).

Effect of Fasting. The presence of food in the gastrointestinal tract decreases absorption of water-soluble Pb (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Maddaloni et al. 1998; Rabinowitz et al. 1980). In adults, absorption of a tracer dose of Pb acetate in water was approximately 63% when ingested by fasted subjects and 3% when ingested with a meal (James et al. 1985). Heard and Chamberlain (1982) reported nearly identical results. The arithmetic mean of reported estimates of absorption in fasted adults was 57% (calculated by ATSDR based on Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980). Reported fed/fasted ratios for absorption in adults range from 0.04 to 0.2 (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Mineral content is one contributing factor to the lower absorption of Pb when Pb is ingested with a meal; in particular, the presence of calcium and phosphate in a meal will depress the absorption of ingested Pb (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain

1982). Suppression of absorption by meals may explain the observation of lower PbB in children (age 3–5 years) who ate breakfast compared to children who went without breakfast, after controlling for nutritional variables (Liu et al. 2011).

Effect of Nutrition. Pb absorption in children is affected by nutritional iron status. Children who are iron deficient have higher PbBs than similarly exposed children who are iron replete, which would suggest that iron deficiency may result in higher absorption of Pb or, possibly, other changes in Pb biokinetics that would contribute to higher PbBs (Mahaffey and Annest 1986; Marcus and Schwartz 1987). Genetic variation in genes involved in iron metabolism appear to affect PbBs; however, it is not certain if these associations are caused by changes in Pb absorption. These include variants in the hemochromatosis (HFE) and transferrin genes, which have been associated with higher PbBs in children (Hopkins et al. 2008), and with lower PbBs and bone Pb levels in elderly men (Wright et al. 2004).

Evidence for the effect for iron deficiency on Pb absorption has been provided from animal studies. In rats, iron deficiency increases the gastrointestinal absorption of Pb, possibly by enhancing binding of Pb to iron binding proteins in the intestine (Bannon et al. 2003; Barton et al. 1978b; Morrison and Quaterman 1987). Interactions between iron and Pb appear to involve either intracellular transfer or basolateral transfer mechanisms. Iron (FeCl₂) added to the mucosal fluid of the everted rat duodenal sac decreases serosal transfer, but not mucosal uptake of Pb (Barton 1984). When mRNA for DMT1, a mucosal membrane carrier for iron (which also transports other divalent metal cations), was suppressed in Caco 2 cells (a human gastrointestinal cell line), the rate of iron and cadmium uptake decreased by 50% compared to cells in which DMT1 mRNA was not suppressed; however, DMT1 mRNA suppression did not alter the rate of Pb uptake by Caco 2 cells, indicating that Pb may enter Caco 2 cells through a mechanism that is independent of DMT1 (Bannon et al. 2003). The above observations suggest that rate-limiting saturable mechanisms for Pb absorption are associated with transfer of Pb from cell to blood rather than with mucosal transfer. Similar mechanisms may contribute to Pb-iron and Pb-calcium absorption interactions in humans, and possibly interactions between Pb and other divalent cations such as cadmium, copper, magnesium, and zinc.

Dietary calcium intake affects Pb absorption. An inverse relationship has been observed between dietary calcium intake and PbBs in children, suggesting that children who are calcium-deficient may absorb more Pb than calcium-replete children (Elias et al. 2007; Mahaffey et al. 1986; Schell et al. 2004; Ziegler et al. 1978). An effect of calcium on Pb absorption is also evident in adults. In experimental studies of adults, absorption of a single dose of Pb (100–300 µg Pb chloride) was lower when the Pb was ingested together

with calcium carbonate (0.2–1 g calcium carbonate) than when the Pb was ingested without additional calcium (Blake and Mann 1983; Heard and Chamberlain 1982). A similar effect of calcium occurs in rats (Barton et al. 1978a). Complexation with calcium (and phosphate) in the gastrointestinal tract and competition for a common transport protein have been proposed as possible mechanisms for this interaction (Barton et al. 1978a; Heard and Chamberlain 1982). Absorption of Pb from the gastrointestinal tract is enhanced by dietary calcium depletion or administration of cholecalciferol (Mykkänen and Wasserman 1981, 1982). This "cholecalciferol-dependent" component of Pb absorption appears to involve a stimulation of the serosal transfer of Pb from the epithelium, not stimulation of mucosal uptake of Pb (Mykkänen and Wasserman 1981, 1982). This is similar to the effects of cholecalciferol on calcium absorption (Bronner et al. 1986; Fullmer and Rosen 1990).

In a study of young children (ages 6–12 months), PbBs increased in association with lower dietary Zn levels (Schell et al. 2004); however, it is not certain if these associations were caused by changes in Pb absorption.

Effect of Pregnancy. Absorption of Pb may increase during pregnancy. Although there is no direct evidence for this in humans, an increase in Pb absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone Pb), to the increase in PbBs that has been observed during the latter half of pregnancy (see Section 3.1.2, *Pb Distribution during Pregnancy and Maternal-Fetal-Infant Transfer*).

Effect of Dose. Pb absorption in humans may be a capacity-limited process, in which case, the percentage of ingested Pb that is absorbed may decrease with increasing rate of Pb intake. Studies, to date, do not provide a firm basis for discerning if the gastrointestinal absorption of Pb is limited by dose. Numerous observations of nonlinear relationships between PbB and Pb intake in humans provide support for the existence of a saturable absorption mechanism or some other capacity-limited process in the distribution of Pb in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984) (see Section 3.1.2, *Pb in Blood* and *Pb in Plasma* for discussion of saturable uptake of Pb in red blood cells). However, in immature swine that received oral doses of Pb in soil, Pb dose-blood Pb relationships were curvilinear, whereas dose-tissue Pb relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for PbB and linearity for tissues) was observed in swine administered Pb acetate intravenously (Casteel et al. 1997, 2006). These results suggest that the nonlinearity in the Pb dose-blood Pb relationship may derive from an effect of Pb dose on some aspect of the biokinetics of Pb other than absorption. In fasted rats, absorption was estimated at 42 and 2% following single oral administration of

1 and 100 mg Pb/kg, respectively, as Pb acetate, suggesting a limitation on absorption imposed by dose (Aungst et al. 1981). Evidence for capacity-limited processes at the level of the intestinal epithelium (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981) suggests that the intake-uptake relationship for Pb is likely to be nonlinear; however, the dose at which absorption becomes appreciably limited in humans is not known.

Effect of Particle Size. Particle size influences the degree of gastrointestinal absorption (Ruby et al. 1999). In rats, an inverse relationship was found between absorption and particle size of Pb in diets containing metallic Pb particles that were ≤ 250 μm in diameter (Barltrop and Meek 1979). Tissue Pb concentration was a 2.3-fold higher when rats ingested an acute dose (37.5 mg Pb/kg) of Pb particles that were < 38 μm in diameter than when rats ingested particles having diameters in the range of 150–250 μm (Barltrop and Meek 1979). Dissolution kinetics experiments with Pb-bearing mine waste soil suggest that surface area effects control dissolution rates for particles sizes of < 90 μm diameter; however, dissolution of 90–250 μm particle size fractions appeared to be controlled more by surface morphology (Davis et al. 1994). Similarly, Healy et al. (1982) found that the solubility of Pb sulfide in gastric acid *in vitro* was much greater for particles that were 30 μm in diameter than for particles that were 100 μm in diameter.

Absorption from Soil. Absorption of Pb from the gastrointestinal tract involves absorptive transport of soluble Pb species (e.g., Pb^{2+}) across the gastrointestinal tract epithelium. In order for Pb to be absorbed from soil, it must first be made bioaccessible in the gastrointestinal tract. The process of rendering soil Pb bioaccessible may involve: (1) physical and/or chemical digestion of the soil particles to expose Pb deposits to gastrointestinal tract fluids; (2) transfer of Pb minerals from exposed surfaces on soil particles to the aqueous environment of the gastrointestinal tract; and (3) chemical transformation of Pb minerals to soluble Pb species (e.g., Pb^{2+}) that are substrates for absorptive transport. Although absorptive transport of Pb occurs predominantly, if not solely, in the upper small intestine, bioaccessibility processes occurring in the stomach appear to be major determinants of Pb absorption.

Adult subjects who ingested soil (particle size < 250 μm) collected from the Bunker Hill National Priorities List (NPL) site absorbed 26% of the resulting 250 $\mu\text{g}/70$ kg body weight Pb dose when the soil was ingested in the fasted state, and 2.5% when the same soil Pb dose was ingested with a meal (Maddaloni et al. 1998). The value reported for fasted subjects (26%) was approximately half that reported for soluble Pb ingested by fasting adults, or approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Measurements of the absorption of soil Pb in infants or children have not been reported.

Absorption of Pb from ingested soils and surface dust has been studied more extensively in animals (Bannon et al. 2009; Barltrop and Meek 1979; Bradham et al. 2016, 2019; Brown et al. 2004; Casteel et al. 1997, 2006; Freeman et al. 1992, 1994, 1996; Healy et al. 1982; Hettiearachchi et al. 2003; Juhasz et al. 2009; Ryan et al. 2004; Weis and Lavelle 1991). These studies have shown that absorption of soil Pb varies depending upon the Pb mineralogy and physical characteristics of the Pb in the soil (e.g., encapsulated or exposed, particle size). Studies conducted in swine and other animal models have provided estimates of relative bioavailability (RBA) of Pb in soils collected from sites impacted by a variety of sources of Pb contamination including ore and ore processing, shooting of Pb munitions, and Pb-based paint (Bannon et al. 2009; Barltrop and Meek 1979; Bradham et al. 2016, 2019; Brown et al. 2004; Casteel et al. 1997, 2006; Freeman et al. 1992, 1994, 1996; Healy et al. 1982; Hettiearachchi et al. 2003; Juhasz et al. 2009; Ryan et al. 2004; Weis and Lavelle 1991). RBA is the ratio of the absolute bioavailability (or absorption fraction) of Pb in soil to that of a water-soluble reference (Pb acetate). RBA has been measured in animal models using various approaches, including measurement of blood and tissue Pb in animals following dosing with soil or Pb acetate. RBA estimates from these studies ranged from 1 to 100% (mean 60%, n=33, calculated by ATSDR). RBAs for soils (sieved to <250 µm) from firing ranges where the predominant form of Pb was Pb carbonate were approximately 100% (Bannon et al. 2009). A soil amended with NIST paint standard (a mixture of Pb carbonate and Pb oxide) had an RBA of 92%. Smelter slag and soils in which the dominant source of Pb was smelter slag had relatively low RBA (14–40%). Galena (lead sulfide) in soil also had relatively low RBA (1–6%).

Casteel et al. (2006) estimated Pb RBA of 19 soils in swine and categorized the RBA according to Pb mineral associations. Electron microprobe analyses of Pb-bearing grains in the various soils revealed that the grains ranged from as small as 1–2 µm up to a maximum of 250 µm (the sieve size used in preparation of the samples) and that Pb was present in a wide range of different mineral associations (phases), including various oxides, sulfides, sulfates, and phosphates. These variations in size and mineral content of the Pb-bearing grains are the suspected cause of variations in the gastrointestinal absorption of Pb from different samples of soil. Based on these very limited data, the RBA of Pb mineral phases were rank-ordered (Table 3-1).

Table 3-1. Ranking of Relative Bioavailability of Lead (Pb) Mineral Phases in Soil^a

Low bioavailability (RBA<0.25)	Medium bioavailability (RBA=0.25–0.75)	High bioavailability (RBA>0.75)
Angelsite Fe(M) oxide Fe(M) sulfate Galena Pb(M) oxide	Pb oxide Pb phosphate	Cerussite Mn(M) oxide

^aEstimates are based on studies of immature swine.

Fe = iron; M = metal; Mn = manganese; RBA = relative bioavailability (compared to Pb acetate)

Source: Casteel et al. 2006

Several studies have shown that elevating the phosphate concentration of soil can decrease soil Pb RBA (Brown et al. 2004; Hettiarachichi et al. 2003; Ryan et al. 2004). The mechanism for the effect is thought to be the formation of a relatively insoluble form of Pb in soil, pyromorphite, which has a low RBA (Scheckel et al. 2013).

Bioaccessibility in Soil and its Relationship to Relative Bioavailability. Empirical evidence supporting the importance of gastric bioaccessibility in Pb absorption comes from studies of relationships between extractability of Pb from soil measured *in vitro* and Pb RBA measured in animals. *In vitro* extractability of Pb from soil (*in vitro* bioaccessibility, IVBA) strongly correlates with RBA measured swine assays when the extraction is performed at gastric pH ($r^2=0.92$, $n=18$; Drexler and Brattin 2007). Bioaccessibility estimates obtained from IVBA assays are sensitive to assay conditions such as pH, liquid:soil ratios, inclusion or absence of food material, and differences in methods used to separate dissolved and particle-bound Pb (e.g., centrifugation versus filtration); as a result, different assays can yield different results when applied to the same soils or surface dusts (Dong et al. 2016; Juhasz et al. 2011; Lu et al. 2011; Roussel et al. 2010; Saikat et al. 2007; Smith et al. 2011; Van de Wiele et al. 2007). For this reason, application of IVBA assays for predicting RBA must be supported by demonstration of a strong correlation between IVBA and RBA (Drexler and Brattin 2007). Even in the absence of validation of RBA predictions, IVBA assays may be useful for predicting relative differences in RBA between soils. For example, the relative change in Pb RBA resulting from treatment of soils with phosphate amendments was predicted from IVBA measurements even though the IVBA assay performed poorly at predicting the actual RBA of the soils (Juhasz et al. 2016). Bioaccessibility measured with IVBA assays has been shown to increase with decreasing particle size (varied from <2,000 to <50 μm) (Juhasz et al. 2011) and increase with increasing soil acidity and organic matter content (Jin et al. 2005).

Dermal Exposure

Inorganic Pb. Dermal absorption of inorganic Pb compounds is generally considered to be much less than absorption by inhalation or oral routes of exposure; however, few studies have provided quantitative estimates of dermal absorption of inorganic Pb in humans, and the quantitative significance of the dermal absorption pathway as a contributor to Pb body burden in humans remains an uncertainty. Pb was detected in the upper layers of the stratum corneum of Pb-battery workers, prior to their shifts and after cleaning of the skin surface (Sun et al. 2002), suggesting adherence and/or possible dermal penetration of Pb. Following skin application of ^{203}Pb -labeled Pb acetate in cosmetic preparations (0.12 mg Pb in 0.1 mL or 0.18 mg Pb in 0.1 g of a cream) to eight male volunteers for 12 hours, absorption was $\leq 0.3\%$, based on whole-body, urine, and blood ^{203}Pb measurements, and was predicted to be 0.06% during normal use of such preparations (Moore et al. 1980). Most of the absorption took place within 12 hours of exposure. Pb also appears to be absorbed across human skin when applied to the skin as Pb nitrate; however, quantitative estimates of absorption have not been reported. Pb (4.4 mg, as Pb nitrate) was applied (vehicle or solvent not reported) to an occluded filter placed on the forearm of an adult subject for 24 hours, after which, the patch was removed, the site cover and the forearm were rinsed with water, and total Pb was quantified in the cover material and rinse (Stauber et al. 1994). The amount of Pb recovered from the cover material and rinse was 3.1 mg (70% of the applied dose). Based on this recovery measurement, 1.3 mg (30%) of the applied dose remained either in the skin or had been absorbed in 24 hours; the amount that remained in or on the skin and the fate of this Pb (e.g., exfoliation) was not determined. Exfoliation has been implicated as an important pathway of elimination of other metals from skin (e.g., inorganic mercury; Hursh et al. 1989). Pb concentrations in sweat collected from the right arm increased 4-fold following the application of Pb to the left arm, indicating that some Pb had been absorbed (amounts of sweat collected or total Pb recovered in sweat were not reported; Stauber et al. 1994). In similar experiments with three subjects, measurements of ^{203}Pb in blood, sweat, and urine, made over a 24-hour period following dermal exposures to 5 mg Pb as ^{203}Pb nitrate or acetate, accounted for $<1\%$ of the applied (or adsorbed) dose (Stauber et al. 1994). This study also reported that absorption of Pb could not be detected from measurements of Pb in sweat following dermal exposure to Pb as Pb carbonate.

Information on relative dermal permeability of inorganic and organic Pb salts of Pb comes from studies of *in vitro* preparations of excised skin; the rank ordering of penetration rates through excised human skin

was: Pb nuolate (Pb linoleic and oleic acid complex) > Pb naphthanate > Pb acetate > Pb oxide (nondetectable) (Bress and Bidanset 1991).

Studies conducted in animals provide additional evidence that dermal absorption of inorganic Pb is substantially lower than absorption from the inhalation or oral route. In a comparative study of dermal absorption of inorganic and organic salts of Pb conducted in rats, approximately 100 mg of Pb was applied in an occluded patch to the shaved backs of rats. Based on urinary Pb measurements made prior to and for 12 days following exposure, Pb compounds could be ranked according to the relative amounts absorbed (i.e., percent of dose recovered in urine; calculated by ATSDR): Pb naphthalene (0.17%), Pb nitrate (0.03%), Pb stearate (0.006%), Pb sulfate (0.006%), Pb oxide (0.005%), and metal Pb powder (0.002%). This rank order (i.e., Pb naphthalene > Pb oxide) is consistent with a rank ordering of penetration rates of inorganic and organic Pb salts through excised skin from humans and guinea pigs: Pb nuolate (Pb linoleic and oleic acid complex) > Pb naphthanate > Pb acetate > Pb oxide (nondetectable) (Bress and Bidanset 1991). The estimates for percent of dose excreted underestimate actual absorption as these estimates do not account for the Pb retained in bone and other tissues.

Following application of Pb acetate to the shaved clipped skin of rats, the concentration of Pb in the kidneys was found to be higher relative to controls, suggesting that absorption of Pb had occurred (Laug and Kunze 1948). This study also observed that dermal absorption of Pb from Pb arsenate was significantly less than from Pb acetate, and that mechanical injury to the skin significantly increased the dermal penetration of Pb.

Organic Pb. Relative to inorganic Pb and organic Pb salts, tetraalkyl Pb compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). A 0.75-mL amount of tetraethyl Pb, which was allowed to spread uniformly over an area of 25 cm² on the abdominal skin of rabbits, resulted in 10.6 mg of Pb in the carcass at 0.5 hours and 4.41 mg at 6 hours (Kehoe and Thamann 1931). Tetraethyl Pb was reported to be absorbed by the skin of rats to a much greater extent than Pb acetate, Pb oleate, and Pb arsenate (Laug and Kunze 1948). Evidence for higher dermal permeability of organic Pb compounds compared to inorganic organic salts of Pb also comes from *in vitro* studies conducted with excised skin. The rank order of absorption rates through excised skin from humans and guinea pigs was as follows: tetrabutyl Pb > Pb nuolate (Pb linoleic and oleic acid complex) > Pb naphthanate > Pb acetate > Pb oxide (nondetectable) (Bress and Bidanset 1991).

3.1.2 Distribution

Inorganic Pb. Absorbed inorganic Pb appears to be distributed in essentially the same manner regardless of the route of absorption (Chamberlain et al. 1978; Kehoe 1987); therefore, the distribution of absorbed Pb (i.e., by any route) is discussed in this section, rather than in separate sections devoted to specific routes of exposure. The expression “body burden” is used here to refer to the total amount of Pb in the body. Most of the available information about the distribution of Pb to major organ systems (e.g., bone, soft tissues) derives from autopsy studies conducted in the 1960s and 1970s and reflect body burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). A more recent autopsy study found lower Pb concentrations in autopsies performed during the period 2004–2013 (Mari et al. 2014). In general, these studies indicate that the distribution of Pb appears to be similar in children and adults, although a larger fraction of the Pb body burden of adults resides in bone. Several models of Pb pharmacokinetics have been proposed to characterize such parameters as intercompartmental Pb exchange rates, retention of Pb in various tissues, and relative rates of distribution among the tissue groups (see Section 3.1.5 for further discussion of models).

Pb in Blood. Concentrations of Pb in blood vary considerably with age, physiology/life stage (e.g., pregnancy, lactation, menopause), and numerous factors that affect exposure to Pb. PbBs in various demographic strata of the U.S. population are periodically estimated from the NHANES. Based on data from NHANES (2015–2016, CDC 2018a), the geometric mean PbB of U.S. adults, age ≥ 20 years, was 0.920 $\mu\text{g/dL}$ (95% CI 0.862, 0.982). The geometric mean PbB of U.S. children, age 1–5 years, was 0.758 (95% CI 0.675, 0.850). PbBs in the United States have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2018a; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989). While historically, the geometric mean PbB in U.S. children has been higher than that of the adult population, recent estimates indicate that geometric means in children have fallen below that of adults.

Pb in Red Blood Cells. Pb in blood is primarily in the red blood cells (99%) (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002). Although the mechanisms by which Pb crosses cell membranes have not been fully elucidated, results of studies in intact red blood cells and red blood cell ghosts indicate that there are two, and possibly three, pathways for facilitated transfer of Pb across the red cell membrane. The major proposed pathway is an anion exchanger that is dependent upon HCO_3^- and is blocked by anion exchange inhibitors (Bannon et al.

2000, Simons 1985, 1986a, 1986b, 1993). A second minor pathway, which does not exhibit HCO_3^- dependence and is not sensitive to anion exchange inhibitors, may also exist (Simons 1986b). Pb and calcium may also share a permeability pathway, which may be a Ca^{2+} -channel (Calderon-Salinas et al. 1999). Pb is transferred out of the erythrocyte by an active transport pathway, most likely a $(\text{Ca}^{2+}, \text{Mg}^{2+})$ -ATPase (Simons 1988).

Pb in erythrocytes binds to several intracellular proteins. ALAD is the primary binding ligand for Pb in erythrocytes (Bergdahl et al. 1997a, 1998; Sakai et al. 1982; Xie et al. 1998). Pb binding to ALAD is saturable; the binding capacity has been estimated to be approximately 85 $\mu\text{g}/\text{dL}$ red blood cells (or approximately 40 $\mu\text{g}/\text{dL}$ whole blood) and the apparent dissociation constant has been estimated to be approximately 1.5 $\mu\text{g}/\text{L}$ (Bergdahl et al. 1998). Two other Pb-binding proteins have been identified in erythrocytes, a 45 kDa protein (K_d 5.5 $\mu\text{g}/\text{L}$) and a smaller protein(s) having a molecular weight <10 kDa (Bergdahl et al. 1996, 1997a, 1998). Of the three principal Pb-binding proteins identified in erythrocytes, ALAD has the strongest affinity for Pb (Bergdahl et al. 1998) and appears to dominate the ligand distribution of Pb (35–84% of total erythrocyte Pb) at blood Pb levels below 40 $\mu\text{g}/\text{dL}$ (Bergdahl et al. 1996, 1998; Sakai et al. 1982). The decrease in hematocrit that occurs in early infancy (51% at birth to 35% at 6 months) may decrease the total binding capacity of blood and PbBs over the first postnatal 6 months (Simon et al. 2007).

Pb binds to and inhibits the activity of ALAD (Gercken and Barnes 1991; Gibbs et al. 1985; Jaffe et al. 2000; Sakai et al. 1982, 1983). Binding of zinc is essential for ALAD activity, and Pb inhibits activity of ALAD by displacing zinc (Jaffe et al. 2000). Synthesis of ALAD appears to be induced in response to inhibition of ALAD and, therefore, in response to binding of Pb to ALAD (Boudene et al. 1984; Fujita et al. 1982). Several mechanisms may participate in the induction of ALAD, including (1) inhibition of ALAD directly by Pb; (2) inhibition by protoporphyrin, secondary to accumulation of protoporphyrin as a result of Pb inhibition of ferrochelatase; and (3) accumulation of ALA (a substrate of ALAD), secondary to inhibition of ALAD, which may stimulate ALAD synthesis in bone marrow cells (Boudene et al. 1984; Fujita et al. 1982).

ALAD is a polymorphic enzyme with two alleles (ALAD 1 and ALAD 2) and three genotypes (ALAD 1,1, ALAD 1,2, and ALAD 2,2) (Battistuzzi et al. 1981, Scinicariello et al. 2007). Numerous studies have examined the relationship between ALAD genotype and PbBs and the results of these studies are mixed with some studies finding higher PbBs in association with the ALAD 2 allele and other studies finding no associations or lower PbBs associated with the ALAD 2 allele (see Section 3.2). One possible

mechanism by which ALAD polymorphism could affect PbBs is by allelic variation in Pb binding to ALAD (Bergdahl et al. 1997b). However, competitive displacement studies with recombinant human ALAD 1 and ALAD 2 did not indicate differences in affinity for Pb relative to zinc (Jaffe et al. 2000).

Pb in Blood Plasma. Pb binds to several constituents in plasma and it has been proposed that Pb in plasma exists in four states: loosely bound to serum albumin or other proteins with relatively low affinity for Pb, complexed to low molecular weight ligands such as amino acids and carboxylic acids, tightly bound to a circulating metalloprotein, and as free Pb^{2+} (Al-Modhefer et al. 1991). Free ionized Pb (i.e., Pb^{2+}) in plasma represents an extremely small percentage of total plasma Pb. The concentration of Pb^{2+} in fresh serum, as measured by an ion-selective Pb electrode, was reported to be 1/5,000 of the total serum Pb (Al-Modhefer et al. 1991). Approximately 40–75% of Pb in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980). Pb also binds to transferrins and γ -globulins (Guo et al. 2014; Ong and Lee 1980). Pb in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine). Other potential low molecular weight Pb-binding ligands in serum may include citrate, cysteamine, ergothioneine, glutathione, histidine, and oxylate (Al-Modhefer et al. 1991).

Saturable binding to red blood cell proteins contributes to curvature to the blood Pb-plasma Pb relationship with an increase in the plasma/blood Pb ratio with increasing PbB (Barbosa et al. 2006a; Bergdahl et al. 1997b, 1998, 1999; DeSilva 1981; Jin et al. 2008; Kang et al. 2009; Manton et al. 2001; Rentschler et al. 2012; Smith et al. 2002; Tian et al. 2013). The curvature becomes evident at PbBs well above 10 $\mu\text{g}/\text{dL}$. As binding sites for Pb in red blood cells become saturated, a larger fraction of the blood Pb is available in plasma to distribute to brain and other Pb-responsive tissues. This contributes to a curvature in the relationship between Pb intake and PbB, with the blood Pb/intake slope decreasing with increasing Pb intake, which has been observed in children (Sherlock and Quinn 1986) and immature swine (Casteel et al. 2006). Saturable binding of Pb to red blood cell proteins also contributes to a curvilinear relationship between blood Pb and urinary Pb, whereas the relationship between plasma Pb concentration and urine Pb is linear (Bergdahl et al. 1997b).

Pb in Bone. In human adults, approximately >90% of the total body burden of Pb is found in the bones. Based on analyses of post-mortem tissues, bone accounted for 94% of the total Pb body burden of adults and 73% of the body burden in children (Barry 1975). Pb concentrations in bone increase with age, indicative of a relatively slow turnover of Pb in adult bone (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968; Wilker et al. 2011). A portion of Pb in bone readily exchanges with the

plasma Pb pool and, as a result, bone Pb is a reservoir for replenishment of Pb eliminated from blood by excretion (Alessio 1988; Behinaein et al. 2012, 2014; Chettle et al. 1991; Hryhorczuk et al. 1985; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976). Pb in adult bone can serve to maintain blood Pb levels long after exposure has ended (Fleming et al. 1997; Inskip et al. 1996; Kehoe 1987; O'Flaherty et al. 1982; Smith et al. 1996). It can also serve as a source of Pb transfer to the fetus when maternal bone is resorbed for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003).

Pb forms highly stable complexes with phosphate and can replace calcium in the calcium-phosphate salt, hydroxyapatite, which comprises the primary crystalline matrix of bone (Bres et al. 1986; Lloyd et al. 1975; Meirer et al. 2011; Miyake 1986; Verbeeck et al. 1981). As a result, Pb deposits in bone during the normal mineralization process that occurs during bone growth and remodeling and is released to the blood during the process of bone resorption (Aufderheide and Wittmers 1992; O'Flaherty 1991b, 1993). During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). The association of Pb uptake and release from bone with the normal physiological processes of bone formation and resorption renders Pb biokinetics sensitive to these processes. Physiological states (e.g., pregnancy, menopause, advanced age) or disease-related states (e.g., osteoporosis, prolonged immobilization) that are associated with increased bone resorption will tend to promote the release of Pb from bone, which, in turn, may contribute to an increase in the concentration of Pb in blood (Berkowitz et al. 2004; Bonithon-Kopp et al. 1985; Garrido Latorre et al. 2003; Hernandez-Avila et al. 2000; Jackson et al. 2010; Markowitz and Weinberger 1990; Mendola et al. 2013; Nash et al. 2004; Nie et al. 2009; Popovic et al. 2005; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995; Thompson et al. 1985).

Two physiological compartments appear to exist for Pb in cortical and trabecular bone, to varying degrees. In one compartment, bone Pb is essentially inert, having an elimination half-time of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of Pb between bone and soft tissue or blood (Rabinowitz et al. 1976). Although a high bone formation rate in early childhood results in the rapid uptake of circulating Pb into mineralizing bone, bone Pb is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty 1995a). Thus, most of the Pb acquired early in life is not permanently fixed in the bone (O'Flaherty 1995a). In general, bone turnover rates decrease as a function of age, resulting in slowly increasing bone Pb levels among adults (Barry 1975; Gross et al. 1975; Schroeder and Tipton 1968).

Bone Pb burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b). An XRF study of tibia Pb concentrations in individuals >10 years old showed a gradual increase in bone Pb after age 20 (Kosnett et al. 1994). In 60–70-year-old men, the total bone Pb burden may be ≥ 200 mg, while children <16 years old have been shown to have a total bone Pb burden of 8 mg (Barry 1975). However, in some bones (i.e., mid femur and pelvic bone), the increase in Pb content plateaus at middle age and then decreases at higher ages; the decrease with age was more pronounced in females (Drasch et al. 1987). Osteoporosis and release of Pb from resorbed bone to blood may contribute to decreasing bone Pb content in females (Gulson et al. 2002).

Evidence for the exchange of bone Pb and soft tissue Pb stores comes from analyses of stable Pb isotope signatures of Pb in bone and blood. A comparison of blood and bone Pb stable isotope signatures in five adults indicated that bone Pb stores contributed to approximately 40–70% of the Pb in blood (Smith et al. 1996). During pregnancy, the mobilization of bone Pb increases, as the bone is resorbed to produce the fetal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood Pb in pregnant women as they came into equilibrium with a novel environmental Pb isotope signature indicated that 10–88% of the Pb in blood may derive from the mobilization of bone Pb store and approximately 80% of cord blood may be contributed from maternal bone Pb (Gulson 2000; Gulson et al. 1997b, 1999c, 2003). The mobilization of bone Pb during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in Pb concentration that has been observed during the later stages of pregnancy (Gulson et al. 1997b, 2016; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Additional evidence for increased mobilization of bone Pb into blood during pregnancy is provided from studies in nonhuman primates and rats (Franklin et al. 1997; Maldonado-Vega et al. 1996). Direct evidence for transfer of maternal bone Pb to the fetus has been provided from stable Pb isotope studies in *Cynomolgus* monkeys (*Macaca fascicularis*) that were dosed with Pb having a different stable isotope ratio than the Pb to which the monkeys were exposed at an earlier age; approximately 7–39% of the maternal Pb burden that was transferred to the fetus appeared to have been derived from the maternal skeleton (Franklin et al. 1997).

In addition to pregnancy, other states of increased bone resorption appear to result in release of bone Pb to blood; these include lactation, osteoporosis, and severe weight loss. Analysis of kinetics of changes in the stable isotope signatures of blood Pb in postpartum women as they came into equilibrium with a novel environmental Pb isotope signature indicated that the release of maternal bone Pb to blood appears to accelerate during lactation (Gulson et al. 2002, 2003, 2004). This is consistent with declines in patella

bone Pb (measured by XRF) during lactation without calcium supplementation (Hernandez-Avila et al. 1996). Similar approaches have detected increased release of bone Pb to blood in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Garrido Latorre et al. 2003; Hernandez-Avila et al. 2000; Korrick et al. 2002; Nash et al. 2004; Popovic et al. 2005; Symanski and Hertz-Picciotto 1995). In a prospective study of women who were scheduled to undergo bilateral oophorectomy for benign conditions, blood and tibia bone Pb (measured by XRF and adjusted for bone mineral density) did not change 6–18 months post-surgery, regardless of whether patients were given estrogen replacement therapy (Berkowitz et al. 2004). Severe weight loss (28% of BMI in 6 months) in women, which increased bone turnover, increased PbB (Riedt et al. 2009).

Pb in Soft Tissues. Several studies have compared soft tissue concentrations of Pb in autopsy samples of soft tissues (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). These studies were conducted in the 1960s and 1970s and, therefore, reflect burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels. A more recent autopsy study found lower Pb concentrations in autopsies performed during the period 2004–2013 (Mari et al. 2014). Average PbBs reported in the adult subjects were approximately 20 µg/dL in the Barry (1975) and Gross et al. (1975) studies, whereas more current estimates of the average for adults in the United States are <5 µg/dL (CDC 2018a). Levels in other soft tissues also appear to have decreased substantially since these studies were reported (Barregård et al. 1999; Mari et al. 2014). For example, average Pb concentrations in kidney cortex of male adults were 0.78 µg/g wet tissue and 0.79 µg/g, as reported by Barry (1975) and Gross et al. (1975), respectively (samples in the Barry study were from subjects who had no known occupational exposures). An analysis of kidney biopsy samples collected in Sweden found that the mean level of Pb in kidney cortex among subjects not occupationally exposed to Pb was 0.18 µg/g (maximum, 0.56 µg/g) (Barregård et al. 1999). Mari et al. (2014) reported a value of 0.18 µg/g for mean kidney Pb concentration in 20 autopsies performed in Spain. In spite of the downward trends in soft tissue Pb levels, the autopsy studies provide a basis for describing the relative soft tissue distribution of Pb in adults and children. Most of the Pb in soft tissue is in liver. Relative amounts of Pb in soft tissues as reported by Schroeder and Tipton (1968), expressed as percent of total soft tissue Pb, were: liver, 33%; skeletal muscle, 18%; skin, 16%; dense connective tissue, 11%; fat, 6.4%; kidney, 4%; lung, 4%; aorta, 2%; and brain, 2% (other tissues were <1%). The highest soft tissue concentrations in adults also occur in liver and kidney cortex (Barry 1975; Gerhardsson et al. 1986, 1995b; Gross et al. 1975; Mari et al. 2014; Oldereid et al. 1993). The relative distribution of Pb in soft tissues, in males and females,

expressed in terms of tissue:liver concentration ratios, were: liver, 1.0 (approximately 1 µg/g wet weight); kidney cortex, 0.8; kidney medulla, 0.5; pancreas, 0.4; ovary, 0.4; spleen, 0.3; prostate, 0.2; adrenal gland, 0.2; brain, 0.1; fat, 0.1; testis, 0.08; heart, 0.07; and skeletal muscle, 0.05 (Barry 1975; Gross et al. 1975). In contrast to Pb in bone, which accumulates Pb with continued exposure in adulthood, concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults (Barry 1975; Treble and Thompson 1997), reflecting a faster turnover of Pb in soft tissue, relative to bone.

Mechanisms by which Pb enters soft tissues have not been fully characterized (Bressler et al. 2005). Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of Pb transfer and suggest that Pb can interact with transport mechanisms for calcium and iron (see Section 3.1.1). Pb can enter cells through voltage-gated L-type Ca^{2+} channels in bovine adrenal medullary cells (Legare et al. 1998; Simons and Pocock 1987; Tomsig and Suszkiw 1991) and through store-operated Ca^{2+} channels in pituitary GH3, glial C3, human embryonic kidney, and bovine brain capillary endothelial cells (Kerper and Hinkle 1997a, 1997b). Anion exchangers may also participate in Pb transport in astrocytes (Bressler et al. 2005). In addition to the small intestine, DMT1 is expressed in the kidney (Canonne-Hergaux et al. 1999); however, little information is available regarding the transport of Pb across the renal tubular epithelium. In Madin-Darby canine kidney cells (MDCK), Pb has been shown to undergo transepithelial transport by a mechanism distinct from the anion exchanger that has been identified in red blood cells (Bannon et al. 2000). The uptake of Pb into MDCK cells was both time and temperature dependent. Overexpression of DMT1 in the human embryonic kidney fibroblast cells (HEK293) resulted in increased Pb uptake compared to HEK293 cells in which DMT1 was not overexpressed (Bannon et al. 2002). Based on this limited information, it appears that DMT1 may play a role in the renal transport of Pb.

Pb in other soft tissues such as kidney, liver, and brain exists predominantly bound to protein. High affinity cytosolic Pb binding proteins have been identified in rat kidney and brain (DuVal and Fowler 1989; Gonick et al. 2011). The Pb binding proteins of rat are cleavage products of $\alpha 2\mu$ -globulin, a member of the protein superfamily known as retinol-binding proteins (Fowler and DuVal 1991). $\alpha 2\mu$ -Globulin is synthesized in the liver under androgen control and has been implicated in the mechanism of male rat hyaline droplet nephropathy produced by certain hydrocarbons (EPA 1991; Swenberg et al. 1989); however, there is no evidence that Pb induces male-specific nephropathy or hyaline droplet nephropathy. The precise role for Pb binding proteins in the toxicokinetics and toxicity of Pb has not been firmly established; however, it has been proposed that binding proteins may serve as a cytosolic Pb "receptor" that, when transported into the nucleus, binds to chromatin and modulates gene

expression (Fowler and DuVal 1991; Mistry et al. 1985, 1986). Other high-affinity Pb binding proteins (Kd approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4, and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Pb also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the Pb in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+} , but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, Pb will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984).

Pb Distribution during Pregnancy and Maternal-Fetal-Infant Transfer. PbBs tend to be lower in pregnant women compared to non-pregnant women of similar age, BMI, iron status, and smoking status (Jain 2013a; Liu et al. 2013). This difference may reflect increased elimination of Pb from the maternal system (Jain 2013b). Maternal PbB changes during and following pregnancy. A U-shaped temporal pattern has been observed in which maternal PbBs decrease during the second trimester and increase during the third trimester and postpartum period (Gulson et al. 2004, 1997b, 2016; Hertz-Picciotto et al. 2000; Lagerkvist et al. 1996; Lamadrid-Figueroa et al. 2006; Rothenberg et al. 1994). Several factors appear to contribute to these changes. During the second trimester, increased plasma volume contributes to hemodilution of maternal blood Pb and a lowering in the PbB (Hyttén 1985). During the third trimester, growth of the fetal skeleton accelerates, which results in increased mobilization of calcium and Pb from the maternal skeleton, increasing maternal PbB (Gulson et al. 1998b, 2003). Postpartum calcium demand increases further during lactation and breastfeeding, which promotes further mobilization of calcium and Pb from bone and sustains or increases maternal PbBs (Gulson et al. 1998b; Hansen 2011; Tellez-Rojo et al. 2002). Increased demand for calcium in the third trimester and postpartum (to supply calcium for breast milk) is also evident from studies of the effects of dietary calcium supplementation during pregnancy. Calcium supplementation of the maternal diet decreased or delayed the onset of the increase in maternal PbB during the third trimester and postpartum period and delayed mobilization of maternal bone Pb in the third trimester (Ettinger et al. 2009; Gulson et al. 2004, 2016; Manton et al. 2003). The increase in PbB associated with late pregnancy was greater in older women who had a longer history of Pb exposure and, presumably, higher bone Pb levels (Miranda et al. 2010). Pb has been detected in follicular fluid at concentrations similar to that in blood plasma (Silberstein et al. 2006).

A portion of the maternal Pb burden is transferred to the placenta and fetus during pregnancy (Esteban-Vasallo et al. 2012; Franklin et al. 1997; Gulson et al. 2003, 2016; Irwind et al. 2019; Kayaalti et al.

2016; Kazi et al. 2014; O'Flaherty 1998; Reddy et al. 2014). Measurements of stable Pb isotope ratios in pregnant women and cord blood, as they came into equilibrium with a novel environmental Pb isotope signature, indicated that approximately 80% of Pb in fetal cord blood appears to derive from maternal bone stores (Gulson et al. 1997b, 1999c, 2000, 2003, 2016). Stable isotope studies have also demonstrated transfer of Pb from the maternal skeleton to fetus in nonhuman primates (Franklin et al. 1997; O'Flaherty 1998). Transplacental transfer of Pb may be facilitated by an increase in the plasma/PbB ratio during pregnancy (Lamadrid-Figueroa et al. 2006; Montenegro et al. 2008).

Fetal and maternal PbBs and placental Pb concentrations are correlated (Amaral et al. 2010; Baeyens et al. 2014; Baranowska-Boisiacka et al. 2016; Carbone et al. 1998; Chen et al. 2014; Goyer 1990; Graziano et al. 1990; Gulson et al. 2016; Kayaalti et al. 2015b; Kazi et al. 2014; Kim et al. 2015; Kordas et al. 2009; Patel and Prabhu 2009; Reddy et al. 2014). Estimates of the maternal/fetal PbB ratio, based on cord blood Pb measurements at the time of delivery, range from 0.7 to 1.0 at mean maternal PbBs ranging from 1 to 9 µg/dL. In one of the larger studies of fetal PbB, maternal and cord PbB were measured at delivery in 888 mother-infant pairs; the cord/maternal ratio was relatively constant, 0.93, over a blood Pb range of approximately 3–40 µg/dL (Graziano et al. 1990). An analysis of data from 159 mother-infant pairs revealed that higher blood pressure and alcohol consumption late in pregnancy were associated with higher concentrations of Pb in cord blood relative to maternal blood, while higher hemoglobin and sickle cell trait were associated with lower cord blood Pb relative to maternal blood Pb (Harville et al. 2005). No associations were found for calcium intake, physical activity, or smoking. Placental Pb concentrations were found to correlate with ALAD polymorphisms, with higher concentrations observed in association with ALAD2 (Kayaalti et al. 2015b).

Maternal Pb is transferred to infants during breastfeeding. Stable Pb isotope dilution studies suggested that Pb in breast milk can contribute substantially to the isotope profile of infant blood (approximately 40–80%; Gulson et al. 1998b). Numerous studies have reported Pb concentrations in maternal blood and breast milk. In general, these studies indicate that Pb concentrations in breast milk are correlated with Pb concentrations in maternal blood or plasma. Milk/maternal concentration ratios are <0.1, although values of 0.9 have been reported (Baranowska-Boisiacka et al. 2016; Counter et al. 2014; Ettinger et al. 2006, 2014; Gulson et al. 1998a; Koyashiki et al. 2010). Ettinger et al. (2004, 2006) assessed factors influencing breast milk Pb concentration in a group of 367 women and found that PbB (mean 8–9 µg/dL; range 2–30) was a stronger predictor of breast milk Pb (mean 0.9–1.4 µg/dL; range 0.2–8 µg/dL) than bone Pb, and that tibia Pb (mean 9.5 µg/g; range <1–76.5 µg/dL) was a stronger predictor of breast milk Pb than patella bone Pb (mean 14.6 µg/dL; range <1–67.2 µg/dL). Dietary intake of polyunsaturated fatty

acids (PUFA) may decrease transfer of Pb from bone to breast milk (Arora et al. 2008). Pb concentrations in maternal blood and breast milk have been shown to correlate with PbBs in breastfeeding infants (Ettinger et al. 2014; Farhat et al. 2013). Breast milk Pb concentrations explained 37% of the variation in infant blood Pb of breastfeeding infants (Ettinger et al. 2014).

Organic Pb. Information on the distribution of Pb in humans following exposures to organic Pb is extremely limited. One hour following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl or tetramethyl Pb (1 mg/m^3), approximately 50% of the ^{203}Pb body burden was associated with liver and 5% was associated with kidney; the remaining ^{203}Pb was widely distributed throughout the body (Heard et al. 1979). The kinetics of ^{203}Pb in blood of these subjects showed an initial declining phase during the first 4 hours (tetramethyl Pb) or 10 hours (tetraethyl Pb) after the exposure, followed by a phase of gradual increase in PbB that lasted for up to 500 hours after the exposure. Radioactive Pb in blood was highly volatile immediately after the exposure and transitioned to a nonvolatile state thereafter. These observations may reflect an early distribution of organic Pb from the respiratory tract, followed by a redistribution of de-alkylated Pb compounds (see Section 3.1.3 for further discussion of alkyl Pb metabolism).

In a man and woman who accidentally inhaled a solvent containing 31% tetraethyl Pb (17.6% Pb by weight), Pb concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart (Bolanowska et al. 1967). In another incident, a man ingested a chemical containing 59% tetraethyl Pb (38% Pb w/w); Pb concentration was highest in the liver followed by kidney, pancreas, brain, and heart (Bolanowska et al. 1967).

3.1.3 Metabolism

Inorganic Pb. Metabolism of inorganic Pb consists of formation of complexes with a variety of protein and nonprotein ligands (see Section 3.1.2 for further discussion). Major extracellular ligands include albumen and nonprotein sulfhydryls. The major intracellular ligand in red blood cells is ALAD. Pb also forms complexes with proteins in the cell nucleus and cytosol.

Organic Pb. Alkyl Pb compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450. Relatively few studies that address the metabolism of alkyl Pb compounds in humans have been reported. Studies of workers who were exposed to tetraethyl Pb have shown that tetraethyl Pb is excreted in the urine as diethyl Pb, ethyl Pb, and inorganic Pb (Turlakiewicz

and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994). Trialkyl Pb metabolites were found in the liver, kidney, and brain following exposure to the tetraalkyl compounds in workers; these metabolites have also been detected in brain tissue of nonoccupational subjects (Bolanowska et al. 1967; Nielsen et al. 1978). In volunteers exposed by inhalation to 0.64 and 0.78 mg Pb/m³ of ²⁰³Pb-labeled tetraethyl and tetramethyl Pb, respectively, Pb was cleared from the blood within 10 hours, followed by a re-appearance of radioactivity back into the blood after approximately 20 hours (Heard et al. 1979). The high level of radioactivity initially in the plasma indicates the presence of tetraalkyl/trialkyl Pb. The subsequent rise in blood radioactivity, however, probably represents water-soluble inorganic Pb and trialkyl and dialkyl Pb compounds that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

3.1.4 Excretion

Independent of the route of exposure, absorbed Pb is excreted primarily in urine and feces; sweat, saliva, hair and nails, breast milk, and seminal fluids are minor routes of excretion (Chamberlain et al. 1978; Griffin et al. 1975; Hernandez-Ochoa et al. 2005; Hursh and Suomela 1968; Hursh et al. 1969; Kehoe 1987; Rabinowitz et al. 1976; Sears et al. 2012; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed Pb (fecal/urinary excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of submicron Pb particles (Chamberlain et al. 1978; Hursh et al. 1969). Contributors to fecal excretion may include secretion into the bile, gastric fluid, and saliva (Rabinowitz et al. 1976). Biliary excretion of Pb has been observed in the dog, rat, and rabbit (Klaassen and Shoeman 1974; O'Flaherty 1993).

Mechanisms by which inorganic Pb is excreted in urine have not been fully characterized. Such studies have been hampered by the difficulties associated with measuring ultrafilterable Pb in plasma and thereby in measuring the GFR of Pb. Renal plasma clearance was approximately 20–30 mL/minute in a subject who received a single intravenous injection of a ²⁰³Pb chloride tracer (Chamberlain et al. 1978). Urinary Pb excretion is strongly correlated with the GFR of Pb (Araki et al. 1986) and plasma Pb concentration (Bergdahl et al. 1997b; Rentschler et al. 2012) (i.e., urinary excretion is proportional to GFR x plasma Pb concentration). Estimates of plasma-to-urine clearance of Pb range from 13 to 22 L/day, with a mean of 18 L/day (Araki et al. 1986; Manton and Cook 1984; Manton and Malloy 1983; Chamberlain et al. 1978). The rate of urinary excretion of Pb was less than the GFR of ultrafilterable Pb, suggesting renal tubular reabsorption of Pb from the glomerular filtrate (Araki et al. 1986, 1990). Measurement of the renal

clearance of ultrafilterable Pb in plasma indicates that in dogs, Pb undergoes glomerular filtration and net tubular reabsorption (Araki et al. 1986, 1990; Vander et al. 1977; Victory et al. 1979). Net tubular secretion of Pb has been demonstrated in dogs made alkalotic by infusions of bicarbonate (Victory et al. 1979). Renal clearance of blood Pb increases with increasing PbBs >25 µg/dL (Chamberlain 1983). The mechanism for this has not been elucidated and could involve a shift in the distribution of Pb in blood towards a fraction having a higher GFR (e.g., lower molecular weight complex), a capacity-limited mechanism in the tubular reabsorption of Pb, or the effects of Pb-induced nephrotoxicity on Pb reabsorption. Renal clearance of blood Pb has been estimated in approximately 7,600 subjects who participated in the NHANES 2009–2016 (Diamond et al. 2019). Blood Pb concentrations ranged from 0.05 to 34 µg/dL, with medians of 0.54 µg/dL in adolescents (12–<20 years old) and 1.08 µg/dL in adults (≥20 years old). The median blood Pb clearance was 0.043 L/day in adolescents and 0.040 L/day in adults. Blood Pb clearance was approximately 3% of GFR, estimated from creatinine clearance.

Excretion and Routes of Exposure

Inhalation Exposure

Inorganic Pb. Inorganic Pb inhaled as submicron particles is deposited primarily in the bronchiolar and alveolar regions of the respiratory tract, from where it is absorbed and excreted primarily in urine and feces (Chamberlain et al. 1978; Hursh et al. 1969; Kehoe 1987). Fecal/urinary excretion ratios were approximately 0.5 following inhalation of submicron Pb-bearing particles (Chamberlain et al. 1978; Hursh et al. 1969). Higher fecal-urinary ratios would be expected following inhalation of larger particle sizes (e.g., >1 µm) as these particles would be cleared to the gastrointestinal tract from where a smaller percentage would be absorbed (Kehoe 1987; see Section 3.1.1).

Organic Pb. Pb derived from inhaled tetraethyl and tetramethyl Pb is excreted in exhaled air, urine, and feces (Heard et al. 1979). Following 1–2-minute inhalation exposures to ²⁰³Pb tetraethyl (1 mg/m³), in four male subjects, 37% of inhaled ²⁰³Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). In a similar experiment conducted with (²⁰³Pb) tetramethyl Pb, 51% of the inhaled ²⁰³Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. Pb that was not exhaled was excreted in urine and feces. Fecal/urinary excretion ratios were 1.8 following exposure to tetraethyl Pb and 1.0 following exposure to tetramethyl Pb (Heard et al. 1979). Occupational monitoring studies of workers who were exposed to tetraethyl Pb have shown that tetraethyl Pb is excreted in the urine as

diethyl Pb, ethyl Pb, and inorganic Pb (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

Oral Exposure

Inorganic Pb. Much of the available information on the excretion of ingested Pb in adults derives from studies conducted on five male adults who received daily doses of ^{207}Pb nitrate for periods up to 210 days (Rabinowitz et al. 1976). The dietary intakes of the subjects were reduced to accommodate the tracer doses of ^{207}Pb without increasing daily intake, thus preserving a steady state with respect to total Pb intake and excretion. Total Pb intakes (diet plus tracer) ranged from approximately 210 to 360 $\mu\text{g}/\text{day}$. Urinary excretion accounted for approximately 12% of the daily intake (range for five subjects: 7–17%) and fecal excretion, approximately 90% of the daily intake (range, 87–94%). Based on measurements of tracer and total Pb in saliva, gastric secretions, bile, and pancreatic secretions (samples collected from three subjects by intubation), gastrointestinal secretion of Pb was estimated to be approximately 2.4% of intake (range, 1.9–3.3%). In studies conducted at higher ingestion intakes, 1–3 mg/day for up to 208 weeks, urinary Pb excretion accounted for approximately 5% of the ingested dose (Kehoe 1987). Elimination of Pb is multiphasic, reflecting pools of Pb in the body that have varying retention times. Elimination from blood and soft tissues is faster than bone (Nilsson et al. 1991; Rabinowitz et al. 1976). As a result, after an abrupt decrease in exposure, PbB declines at an apparent rate that reflects excretion of Pb from blood and replenishment of Pb in blood from bone stores. The elimination half-time of Pb in blood in retired Pb workers was tri-exponential, with approximately 22% of elimination occurring at a half-time of 34 days (95% CI: 29, 41), 28% at a half-time of 1.2 years (95% CI: 0.85, 1.8), and 50% at a half-time of 13 years (95% CI: 10, 18) (Nilsson et al. 1991). The corresponding mono-exponential half-time for finger bone (XRF) in these same subjects was 16 years (85% CL 12, 23). Apparent elimination half-times for blood Pb in children also vary considerably, dependent in part on age and exposure history of the child that establishes levels of Pb in bone (Manton et al. 2000; Specht et al. 2018). Manton et al. (2000) estimated apparent elimination half-times for PbB in children (ages 2–3 years at time of exposure) that ranged from 8 to 38 months. However, these estimates reflect both excretion of Pb from blood as well as transfer of Pb from bone to blood; the latter would tend to increase the apparent blood elimination half-time. Specht et al. (2018) estimated blood Pb elimination half-times for Pb transferred from bone to blood (estimated with XRF measurements and biokinetics modeling). Estimated blood Pb half-times were 6.9 ± 4 (SD) days in children 1–3 years old and 19.3 ± 14.1 days in children >3 years old (Specht et al. 2018).

Dermal Exposure. Inorganic Pb is excreted in sweat and urine following dermal exposure to Pb nitrate or Pb acetate (Moore et al. 1980; Stauber et al. 1994).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Early Pb modeling applications relied on classical pharmacokinetics. Compartments representing individual organs or groups of organs that share a common characteristic were defined as volumes, or pools, that are kinetically homogeneous. For example, the body could be represented by a central compartment (e.g., blood plasma), and one or two peripheral compartments, which might be “shallow” or “deep” (i.e., they may exchange relatively rapidly or relatively slowly with blood plasma) (O’Flaherty 1987). One of the first of such models was proposed by Rabinowitz et al. (1976) based on a study of the kinetics of ingested stable Pb isotope tracers and Pb balance data in five healthy adult males. The Rabinowitz model included three compartments: a central compartment representing blood and other tissues and spaces in rapid equilibrium with blood (e.g., interstitial fluid); a shallow tissue compartment, representing soft tissues and rapidly exchanging pools within the skeleton; and a deep tissue compartment, representing, primarily, slowly exchanging pools of Pb within bone. Excretion pathways represented in the model included urinary, from the central compartment, and bile, sweat, hair, and nails, from the shallow tissue compartment. The model predicted pseudo-first-order half-times for Pb of approximately 25, 28, and 10^4 days in the central, shallow tissue, and deep compartments, respectively. The slow kinetics of the deep tissue compartment led to the prediction that it would contain most of the Pb burden after lengthy exposures (e.g., years), consistent with Pb measurements made in human autopsy samples (see Section 3.1.2 Distribution). Note that this model did not simulate the distribution of Pb within blood (e.g., erythrocytes and plasma), nor did it simulate subcompartments within bone or physiological processes of bone turnover that might affect kinetics of the deep tissue compartment.

Marcus (1985b) reanalyzed the data from stable isotope tracer studies of Rabinowitz et al. (1976) and derived an expanded multicompartment kinetic model for Pb that included separate compartments for cortical (slow, $t_{1/2}$ 1.2×10^4 – 3.5×10^4 days) and trabecular (fast, $t_{1/2}$ 100–700 days), an approach subsequently adopted in several models (Bert et al. 1989; EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a). A more complex representation of the Pb disposition in bone included explicit simulation of diffusion of Pb within the bone volume of the osteon and exchange with blood at the canaliculus (Marcus 1985a). The bone diffusion model was based on Pb kinetics data from studies conducted in dogs. Marcus (1985c) also introduced nonlinear kinetics of exchange of Pb between plasma and erythrocytes. The blood model included four blood subcompartments: diffusible Pb in plasma, protein-bound Pb in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool. This model predicted the curvilinear relationship between plasma and PbBs observed in humans (see Section 3.1.2 Distribution for further discussion of plasma-erythrocyte Pb concentrations).

Additional information on Pb biokinetics, bone mineral metabolism, and Pb exposures has led to further refinements and expansions of these earlier modeling efforts. Four pharmacokinetic models, in particular, are currently being used or are being considered for broad application in Pb risk assessment: (1) the O'Flaherty Model, which simulates Pb kinetics from birth through adulthood (O'Flaherty 1993, 1995a); (2) the EPA Integrated Exposure Uptake BioKinetic (IEUBK) Model for Lead in Children developed by EPA (1994a, 1994b); (3) the Leggett Model, which simulates Pb kinetics from birth through adulthood (Leggett 1993); and (4) the EPA All Ages Lead Model (AALM, EPA 2014a). The AALM is currently under review by EPA; a version of the model is available at <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=343670> (January 10, 2020). The structure and parameterization of the O'Flaherty Model is distinct from both the IEUBK Model and Leggett Model. The AALM is an update of the O'Flaherty and Leggett models, extended to include a multi-media exposure model.

The IEUBK Model simulates multimedia exposures, uptake, and kinetics of Pb in children ages 0–7 years for predicting pseudo-steady state relationships between Pb exposure and PbB; the model is not intended for use in predicting short-term kinetics of blood Pb or Pb concentrations in tissues other than whole blood. The O'Flaherty Model, Leggett Model, and AALM are lifetime models, and include parameters that simulate uptake and kinetics of Pb during infancy, childhood, adolescence, and adulthood. Pb exposure (e.g., residence-specific environmental Pb concentrations, childhood activity patterns) is not readily described by current versions of the O'Flaherty and Leggett models. The IEUBK Model and AALM include parameters for simulating exposures and uptake to estimate average daily uptake of Pb

(µg/day) among populations potentially exposed via soil and dust ingestion, air inhalation, tap water ingestion, diet, and miscellaneous (other) intakes. All four models have been calibrated, to varying degrees, against empirical physiological data on animals and humans, and data on PbBs in individuals and/or populations (Beck et al. 2001; Bowers and Mattuck 2001; Cal EPA 2013; EPA 1994a, 1994c, 2014a, 2014b, 2016; Griffin et al. 1999; Hogan et al. 1998; Leggett 1993; Li et al. 2016a; MacMillan et al. 2015; O'Flaherty 1993, 1995a, 1998, 2000; Pounds and Leggett 1998; White et al. 1998; Von Lindern et al. 2003, 2016).

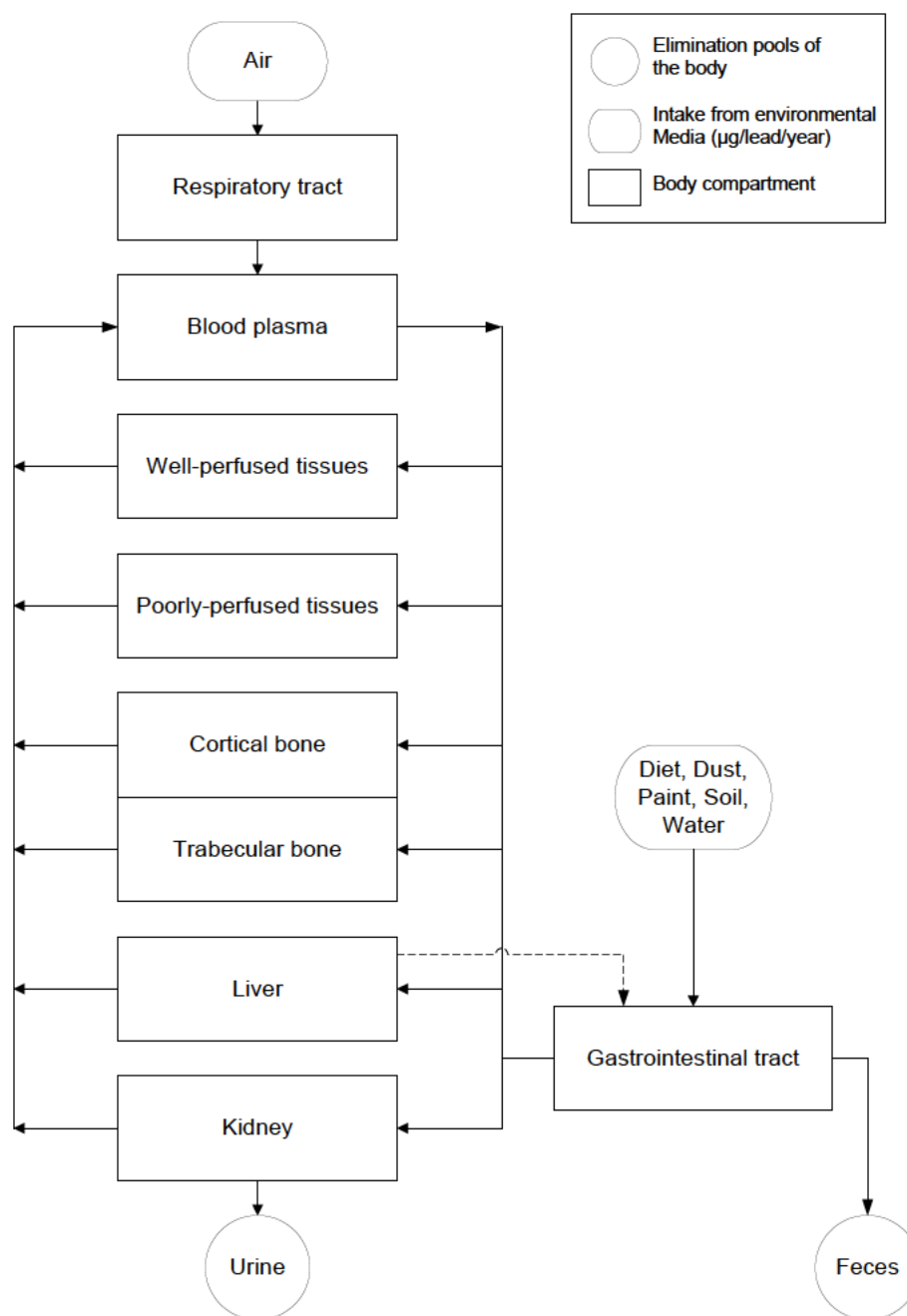
The focus on relying on PbBs for model evaluation and calibration derives from several concerns. The empirical basis for a relationship between low levels of Pb exposure and behavioral dysfunction largely consists of prospective epidemiological studies relating various indices of dysfunction with PbB (see Section 3.3). In this context, PbB has been related to health effects of Pb, and this is the main reason that the focus of interest in the models has been on estimating PbBs. Also, the most available data with which to calibrate and validate the models have been data relating exposure and/or Pb intake to blood concentration. Thus, there is greater confidence in the validity of the models for estimating blood concentrations, rather than Pb levels in other physiologic compartments. Although the principal adverse health effects of Pb have been related to concentrations of Pb in blood, other biomarkers of Pb exposure, such as bone Pb concentrations, are also of value in assessing associations between Pb exposure and health; hence, there is a need for models that predict concentrations of Pb in tissues other than blood (see Section 3.3).

The following four pharmacokinetic models are discussed in great detail below: (1) the O'Flaherty Model (O'Flaherty 1993, 1995a); (2) the IEUBK Model for Lead in Children (EPA 1994a, 1994b); (3) the Leggett Model (Leggett 1993); and (4) AALM (EPA 2014a).

3.1.5.1 O'Flaherty Model

The O'Flaherty Model simulates Pb exposure, uptake, and disposition in humans, from birth through adulthood (O'Flaherty 1993, 1995a). Figure 3-1 shows a conceptualized representation of the O'Flaherty Model, including the movement of Pb from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between blood plasma, liver, kidney, richly-perfused tissues, poorly-perfused tissues, bone compartments, and excretion from liver and/or kidney. The model simulates both age- and media-specific absorption. Because many of the pharmacokinetic functions are based on body weight and age, the model can be used to estimate PbBs

Figure 3-1. Compartments and Pathways of Lead (Pb) Exchange in the O'Flaherty Model*



*Schematic model for Pb kinetics in which Pb distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone. The model simulates tissue growth with age, including growth and resorption of bone mineral.

Sources: O'Flaherty 1991b, 1993, 1995a

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across a broad age range, including infants, children, adolescents, and adults. The model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood, soft tissues, and bone that determine the disposition of Pb in the human body.

A central feature of the model is the growth curve, a logistic expression relating body weight to age. The full expression relating weight to age has five parameters (constants), so that it can readily be adapted to fit a range of standardized growth curves for men and women. Tissue growth and volumes are linked to body weight; this provides explicit modeling of concentrations of Pb in tissues. Other physiologic functions (e.g., bone formation) are linked to body weight, age, or both.

Pb exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). Uptake and release of Pb from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively. Rates of bone formation and resorption are simulated as age-dependent functions, which gives rise to an age-dependence of Pb kinetics in bone. The model simulates an age-related transition from immature bone, in which bone turnover (formation and resorption) rates are relatively high, to mature bone, in which turnover is relatively slow. Changes in bone mineral turnover associated with senescence (e.g., postmenopausal osteoporosis) are not represented in the model. In addition to metabolically active regions of bone, in which Pb uptake and loss is dominated by bone formation and loss, a region of slow kinetics in mature cortical bone is also simulated, in which Pb uptake and release to blood occur by heteroionic exchange with other minerals (e.g., calcium). Heteroionic exchange is simulated as a radial diffusion in bone volume of the osteon. All three processes are linked to body weight, or the rate of change of weight with age. This approach allows for explicit simulation of the effects of bone formation (e.g., growth) and loss, changes in bone volume, and bone maturation on Pb uptake and release from bone. Exchanges of Pb between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of Pb in erythrocytes; this replicates the curvilinear relationship between plasma and erythrocyte Pb concentrations observed in humans (see Section 3.1.2). Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of GFR. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively.

The O'Flaherty Model simulates Pb intake from inhalation and ingestion. Inhalation rates are age-dependent. Absorption of inhaled Pb is simulated as a fraction (0.5) of the amount inhaled, and is

independent of age. The model simulates ingestion exposures from infant formula, soil and dust ingestion, and drinking water ingestion. Rates of soil and dust ingestion are age-dependent, increasing to approximately 130 mg/day at age 2 years, and declining to <1 mg/day after age 10 years. Gastrointestinal absorption of Pb in diet and drinking water is simulated as an age-dependent fraction, declining from 0.58 of the ingestion rate at birth to 0.08 after age 8 years. These values can be factored to account for relative bioavailability when applied to absorption of Pb ingested in dust or soil.

The O'Flaherty Model, as described in O'Flaherty (1993, 1995a), utilizes point estimates for parameter values and yields point estimates as output; however, a subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability in exposure, absorption, and erythrocyte Pb binding capacity (Beck et al. 2001). This extension of the model can be used to predict the probability that children exposed to Pb in environmental media will have PbBs exceeding a health-based reference value (e.g., 5 µg/dL).

The model was designed to operate with an exposure time step on 1 year (the smallest time interval for a single exposure event). However, the implementation code allows constructions of simulations with an exposure time step as small as 1 day, which would allow simulation of rapidly changing intermittent exposures (e.g., an acute exposure event).

The O'Flaherty Model was initially calibrated to predict blood, bone, and tissue Pb concentrations in rats (O'Flaherty 1991a), and subsequently modified to reflect anatomical and physiological characteristics in children (O'Flaherty 1995a), adults (O'Flaherty 1993), and Cynomolgus monkeys (*M. fascicularis*) (O'Flaherty et al. 1998). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. Comparisons of predicted and observed PbB in children and adults are reported in O'Flaherty (1993, 1995a). MacMillan et al. (2015) evaluated performance of the model for predicting population blood and bone Pb levels in a convenience sample of 263 individuals (age range 1–83 years) who experienced low chronic exposure. Based on this evaluation, model performance for predicting general trends in population PbBs and cortical bone Pb concentrations was improved by revising parameters that determine binding of Pb in red blood cells. Revisions included decreasing the maximum and affinity constants (*BIND* and *KBIND*, respectively) and increasing clearance of Pb from blood to bone by increasing the permeability constant for Pb diffusion across the canaliculi-bone interface from canaliculi to bone (*P₀*).

3.1.5.2 EPA IEUBK Model

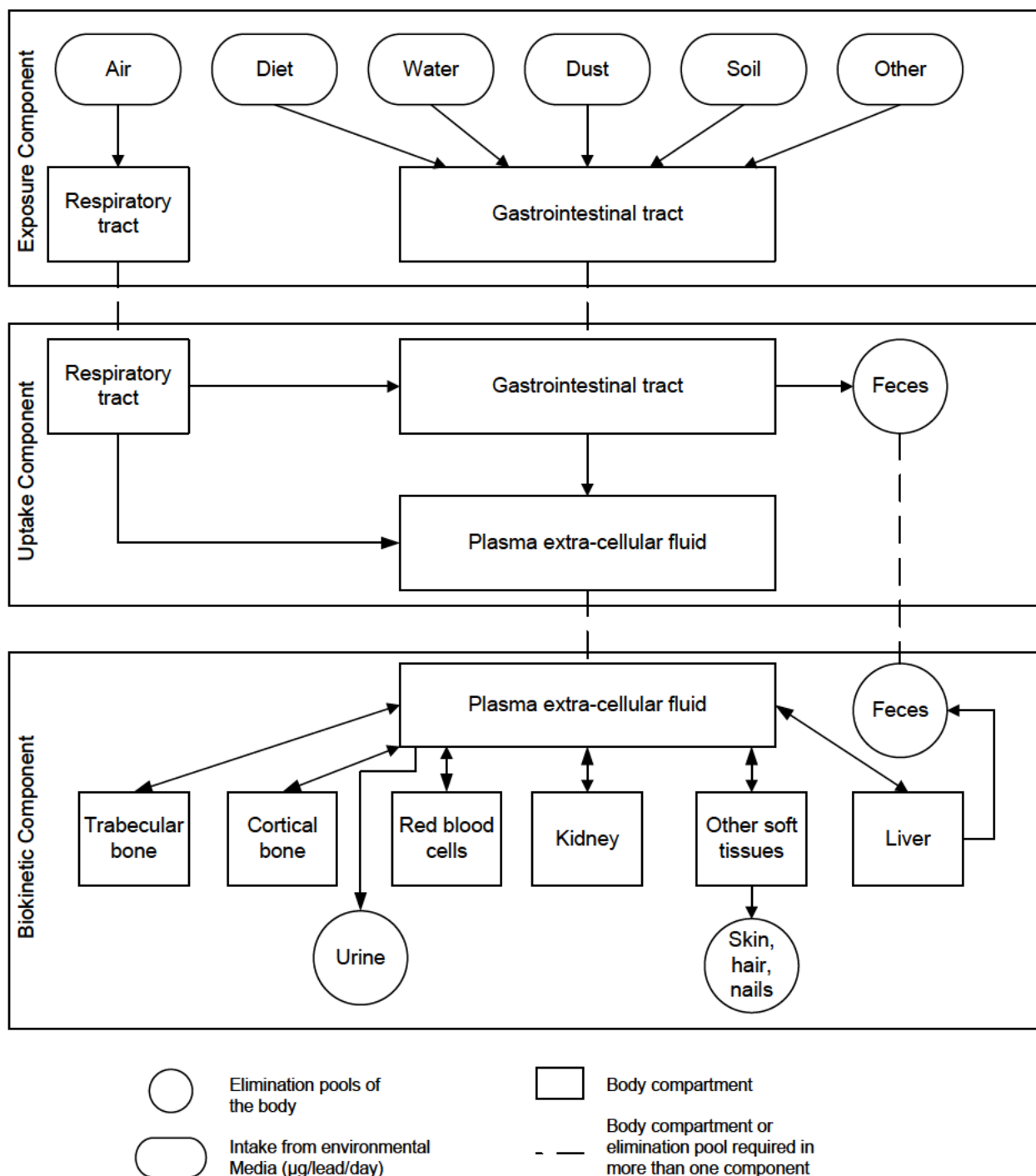
The EPA IEUBK Model for Lead in Children simulates Pb exposure, uptake, and disposition in human children from birth to age 7 years (EPA 1994a, 1994b, 2002a; White et al. 1998). Figure 3-2 shows a conceptualized representation of the IEUBK Model. The model has four major submodels: (1) exposure model, in which average daily intakes of Pb ($\mu\text{g}/\text{day}$) are calculated for each inputted exposure concentration (or rates) of Pb in air, diet, dust, soil, and water; (2) uptake model, which converts environmental media-specific Pb intake rates calculated from the exposure model into a media-specific time-averaged uptake rate ($\mu\text{g}/\text{day}$) of Pb to the central compartment (blood plasma); (3) biokinetic model, which simulates the transfer of absorbed Pb between blood and other body tissues, elimination of Pb from the body (via urine, feces, skin, hair, and nails), and predicts an average PbB for the exposure time period of interest; and (4) blood Pb probability model, which applies a log-normal distribution (using geometric mean and geometric standard deviation for parameters) to predict probabilities for the occurrence of a specified given PbB in a population of similarly exposed children.

Exposure Model. The exposure model simulates intake of Pb ($\mu\text{g}/\text{day}$) for inputted exposures to Pb in air ($\mu\text{g}/\text{m}^3$), drinking water ($\mu\text{g}/\text{L}$), soil-derived dust ($\mu\text{g}/\text{g}$), or diet ($\mu\text{g}/\text{day}$). The exposure model operates on a 1-year time step, the smallest time interval for a single exposure event. The model accepts inputs for media intake rates (e.g., air volumes, breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway is partitioned in exposures to outdoor air and indoor air, with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to Pb to soil-derived dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates Pb absorption for the gastrointestinal tract as the sum of capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear relationship). These two terms are intended to represent two different mechanisms of Pb absorption, an approach that is in accord with limited available data in humans and animals that suggest a capacity limitation to Pb absorption (see Section 3.2.1). One of the parameters for the capacity-limited absorption process (that represents that maximum rate of absorption) is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested Pb as a function of total Pb intake as well as an age-dependence of fractional Pb absorption. Absorption

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Figure 3-2. Structure of the IEUBK Model for Lead (Pb) in Children*



*Schematic for integrated Pb exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake (i.e., absorption into the plasma-extracellular fluid), tissue distribution, and excretion).

Sources: EPA 1994a, 1994b

fractions are also medium-specific. At 30 months of age, at low intakes ($<200 \mu\text{g/day}$), below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested Pb in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, $>5,000 \mu\text{g/day}$). For Pb ingested in soil or dust, fractional absorption is 0.35 at low intakes ($<200 \mu\text{g/day}$) and decreases to 0.09 (intake, $>5,000 \mu\text{g/day}$).

The uptake model assumes that 32% of inhaled Pb is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active Pb smelter ($<1 \mu\text{m}$, 12.5%; $1\text{--}2.5 \mu\text{m}$, 12.5%; $2\text{--}15 \mu\text{m}$, 20%; $15\text{--}30 \mu\text{m}$, 40%; $>30 \mu\text{m}$, 15%); size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions. Pb deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas Pb deposited in the nasopharyngeal and tracheobronchial regions (30–80% of the Pb particles in the size range $1\text{--}15 \mu\text{m}$) is assumed to be transported to the gastrointestinal tract.

Biokinetics Model. The biokinetics model includes a central compartment, six peripheral body compartments, and three elimination pools (urine, feces, lumped pool representing skin, hair, and nails). The body compartments include plasma and extracellular fluid (central compartment), red blood cells, kidney, liver, trabecular bone, cortical bone, and other soft tissue (EPA 1994a). The model simulates growth of the body and tissues, compartment volumes, and Pb masses and concentrations in each compartment. PbB at birth (neonatal) is assumed to be 0.85 of the maternal blood Pb. Neonatal Pb masses and concentrations are assigned to other compartments based on a weighted distribution of the neonatal PbB. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of Pb into erythrocytes is simulated, with a maximum erythrocyte Pb concentration of $12 \mu\text{g/dL}$. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway representing losses from skin, hair and nail, from the other soft tissue compartment.

Blood Pb Probability Model. Inputs to the IEUBK Model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central tendency estimate of PbB for children who might experience the inputted exposures. However, within a group of

similarly exposed children, PbBs would be expected to vary among children as a result of inter-individual variability in media intakes, absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of PbB for which the geometric mean is given by the central tendency PbB outputted from the biokinetics model and the GSD is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given PbB within a population of similarly exposed children. The model can be iterated for varying exposure concentrations (e.g., a series of increasing soil Pb concentrations) to predict the media concentration that would be associated with a probability of 0.05 for the occurrence of a PbB exceeding 10 µg/dL. A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability and uncertainty in exposure and absorption (Goodrum et al. 1996; Griffin et al. 1999). This extension of the model provides an alternative to the blood Pb probability model for incorporating, explicitly, estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of PbBs. More recently, Zartarian et al. (2017) provided an analysis coupling the IEUBK model with EPA's Stochastic Human Exposure and Dose Simulation (SHEDS)-Multimedia Model that considered general U.S. childhood exposures probabilistically and assessed primary sources of Pb exposure across the distribution of PbB.

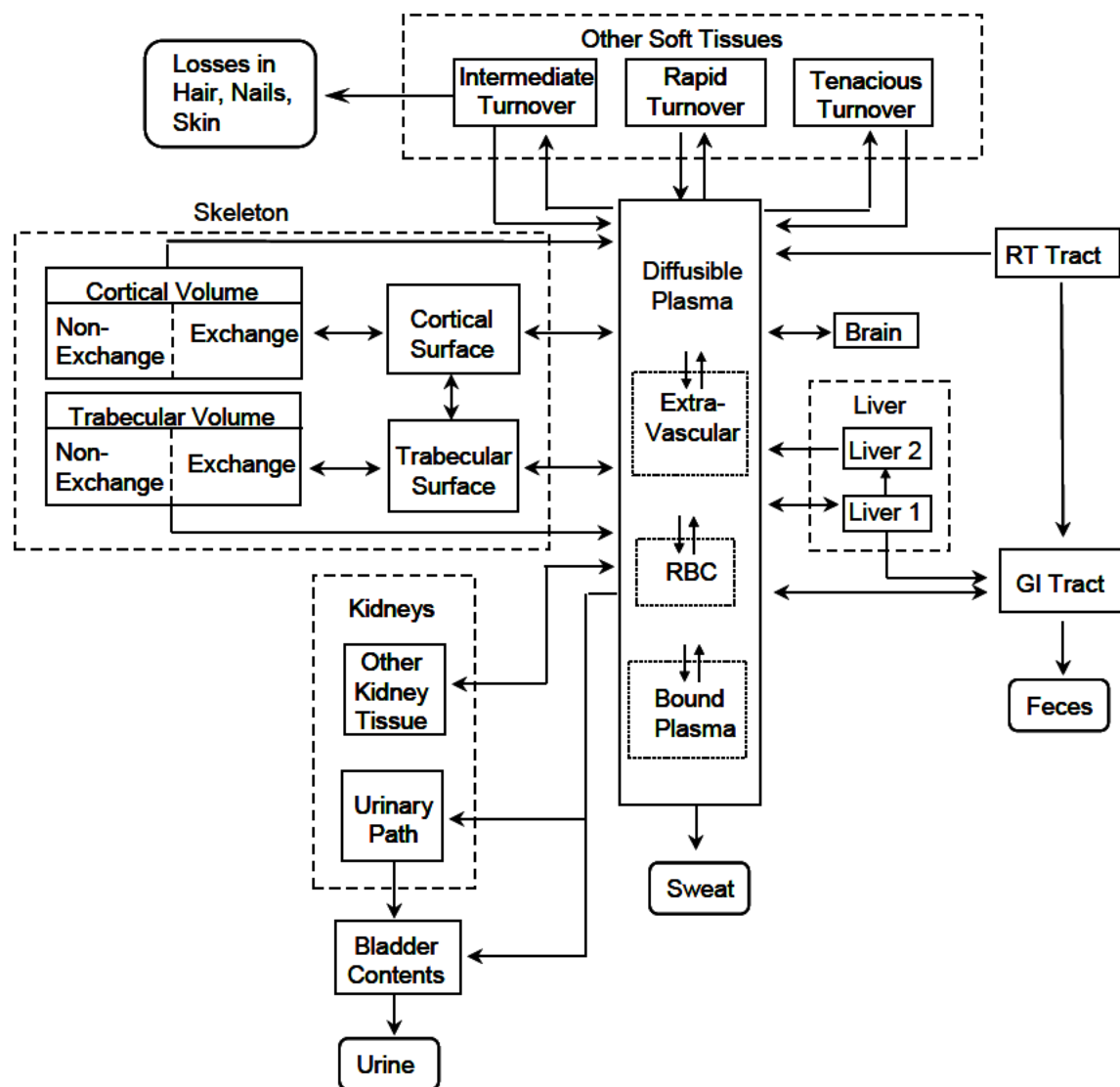
Performance of the IEUBK Model has been evaluated for predicting observed PbBs in children (Hogan et al. 1998; Li et al. 2016a; Von Lindern et al. 2003, 2016). The largest evaluation utilized longitudinal exposure and blood Pb data for approximately 2,200 children who resided near a former smelter in northern Idaho (Bunker Hill site) during a 14-year period of remediation activities (Von Lindern et al. 2003, 2016). The observed annual blood Pb geometric means ranged from 2.5 to 10.6 µg/dL. The model predicted the time course of the observed PbBs as the remediation progressed when the gastrointestinal absorption fraction was calibrated to agree with blood Pb observations (Von Lindern et al. 2003). A similar outcome was obtained in a subsequent analysis in which the gastrointestinal absorption fraction was adjusted to agree with site measurements of soil Pb RBA, and soil and dust ingestion rates were calibrated to the blood Pb observations (Von Lindern et al. 2016). The mean difference between predicted and observed annual geometric mean PbBs (predicted - observed) was -0.31 µg/dL (range: -1.07, 1.93) and the mean relative percent difference was -8.4% (range: -23–21%). Applications of the IEUBK Model to the Bunker Hill site were reviewed by the National Research Council (NRC 2005). Hogan et al. (1998) evaluated the IEUBK Model performance based on residential exposure and blood data for approximately 478 children who resided near three Pb mining and smelting sites. The observed geometric means for the three sites ranged from 5.2 to 6.8 µg/dL. The IEUBK Model predictions agreed reasonably well with observations for children whose exposures were predominantly

from their residence (e.g., who spent no more than 10 hours/week away from home). The mean difference between predicted and observed site geometric mean PbBs (predicted-observed) was 0.03 µg/dL (range -0.6–0.7) and the mean relative percent difference was -0.4% (range -12–10%). The predicted geometric mean PbBs were within 0.7 µg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have PbBs exceeding 10 µg/dL were within 4% of the observed percentage at each site. Li et al. (2016a) compared predictions of PbB to observations in a cohort of 760 children in Central China. The observed residence area geometric means ranged from 5 to 14 µg/dL. When exposure parameters were set to the study population (e.g., exposure media Pb concentration and intakes), predicted and observed PbBs were not significantly different. The mean difference between predicted and observed geometric mean PbBs for 21 residence areas (predicted-observed) was 0.55 µg/dL (range -2.0–3.2) and the mean relative percent difference was 3.5% (range -32–28%). These evaluations provide support for the validity of the IEUBK Model for estimating PbBs in children at sites where their exposures can be adequately characterized. Similar empirical comparisons of the IEUBK Model have shown that agreement between model predictions and observed PbBs at specific locations is influenced by numerous factors, including the extent to which the exposure and blood Pb measurements are adequately matched, and site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect Pb intake or uptake in children (Bowers and Mattuck 2001; Von Lindern et al. 2003, 2016). In addition to the above empirical comparisons, the computer code used to implement the IEUBK Model (IEUBK version 0.99d) has undergone an independent validation and verification and has been shown to accurately implement the conceptual IEUBK Model (Zaragoza and Hogan 1998).

3.1.5.3 Leggett Model

The Leggett Model simulates Pb intake, absorption, and disposition in humans, from birth through adulthood (Leggett 1993). Figure 3-3 shows a conceptualized representation of the model, including the movement of Pb from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between diffusible blood plasma, soft tissues, bone compartments, and excretion from liver, kidneys, and sweat. A detailed exposure module is not linked to the Leggett Model; rather, Pb exposure estimates are incorporated into the model as age-specific point estimates of average daily intake (µg/day) from inhalation and ingestion. A description of the model and its potential application to risk assessment are provided below.

Figure 3-3. Compartments and Pathways of Lead (Pb) Exchange in the Leggett Model*



*Schematic model for Pb kinetics in which Pb distribution is represented by exchanges between the central plasma-extracellular fluid and tissue compartments. Bone is represented as having surface (which rapidly exchanges with plasma-extracellular fluid) and volume compartments; the latter simulates slow exchange with the surface and slow return of Pb to the plasma-extracellular fluid from bone resorption.

GI = gastrointestinal; RBC = red blood cell; RT = respiratory

Source: Leggett 1993

The Leggett Model includes a central compartment, 15 peripheral body compartments, and 4 elimination pools (urine, feces, sweat, and lumped pool representing skin, hair, and nails), as illustrated in Figure 3-3. Transport of Pb from blood plasma to tissues is assumed to follow first-order kinetics. Transfer rate constants vary with age and PbB. Above a nonlinear threshold concentration in red blood cells (assumed to be 60 µg/dL), the rate constant for transfer to red blood cells declines and constants to all other tissues increase proportionally (Leggett 1993). This replicates the nonlinear relationship between plasma and red blood cells observed in humans (see Section 3.1.2). The model simulates blood volume as an age-dependent function, which allows simulation of plasma and PbBs. Pb masses are simulated in all other tissues (tissue volumes are not simulated).

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. The total transfer rate from diffusible plasma to all destinations combined is assumed to be $2,000 \text{ day}^{-1}$, based on isotope tracer studies in humans receiving Pb via injection or inhalation. Values for transfer rates in various tissues and tissue compartments are based on measured deposition fractions or instantaneous fractional outflows of Pb between tissue compartments (Leggett 1993).

The Leggett Model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) for calculating radiation doses from environmentally important radionuclides, including radioisotopes of Pb (Leggett 1993). The Leggett Model simulates age-dependent bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to Pb where possible. The model simulates both rapid exchange of Pb with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchange Pb with the blood plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Pb enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the blood only when bone is resorbed. Rate constants for transfer of Pb from the nonexchangeable pools and blood plasma vary with age to reflect the age-dependence of bone turnover.

The liver is simulated as two compartments: one compartment has a relatively rapid uptake of Pb from plasma and a relatively short removal half-time (days) for transfers to plasma and to the small intestine by biliary secretion, and a second compartment simulates a more gradual transfer to plasma of approximately 10% of Pb uptake in liver. The kidney is simulated as two compartments: one that exchanges slowly with

blood plasma and accounts for Pb accumulation in kidney tissue, and a second compartment that receives Pb from blood plasma and rapidly transfers Pb to urine, with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates). Other excretory pathways (hair, nails, and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett Model simulates Pb intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled Pb is deposited and absorbed with half-times of 1, 3, 10, and 48 hours. Four percent of the inhaled Pb is assumed to be transferred to the gastrointestinal tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron Pb-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). These assumptions would not necessarily apply to exposures to large airborne particles (see Section 3.1.1). Absorption of ingested Pb is simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years), and to 0.15 after age 25 years.

Output from the Leggett Model has been compared with data in children and adult subjects exposed to Pb in order to calibrate model parameters (Leggett et al. 1993; Pounds and Leggett 1998). Nie et al. (2005) evaluated performance of the Leggett Model for predicting bone Pb concentrations in 539 Pb workers. The data included periodic monitoring of PbBs and XRF bone Pb measurements made in 1994 and 1999. Pb intakes of each individual were calibrated to agree with measured PbBs. The Leggett Model underpredicted observed cortical bone Pb concentrations by a factor of 3–4, and underpredicted trabecular bone Pb concentration by a factor of 12–18. EPA (2014a) evaluated performance of the Leggett Model for predicting PbBs in children and blood and bone Pb concentrations in adults. The evaluation of predictions for children used data on PbBs reported in the NHANES for the years 2007–2008, and required making assumptions about Pb exposures in this population. The Leggett Model overpredicted observed PbBs in children 1–7 years of age by a factor of 2–3. Cal EPA (2013) evaluated the Leggett Model for predicting PbBs in smelter workers whose occupational exposures were interrupted during a workers strike. Pre-hire background Pb intakes and pre-strike intakes were calibrated to agree with measured PbBs and the predicted rate of decline in blood Pb that occurred during the strike period was compared to observations. Cal EPA (2013) reported “the average difference between the measured and predicted post-strike BLL was unacceptably large and indicated significant under-prediction of BLLs”.

The average difference was $>4 \mu\text{g/dL}$ in a cohort that had a mean post-strike PbB of $31 \mu\text{g/dL}$ (no further details were provided). Performance was substantially improved when various parameters were calibrated to the observations. These included parameters that control transfers between plasma and bone and red blood cell saturation (see Cal EPA [2013] for details of parameter value changes). The mean difference between predicted and observed annual geometric mean PbBs (predicted-observed) was $-0.9 \mu\text{g/dL}$ (range -26 – 32) and the mean relative percent difference was -8.8% (range: -55 – 320%). Cal EPA (2013) reported several other evaluations of their recalibrated model, including observed and predicted relationships between plasma and whole PbBs in adults, and predicted distribution of Pb in bone and soft tissues compared to estimates from human autopsy studies.

3.1.5.4 EPA All Ages Lead Model (AALM)

The AALM simulates blood and tissue Pb masses (μg) and concentrations ($\mu\text{g/g}$) resulting from exposures to Pb in air, drinking water, surface dust (e.g., indoor dust, soil dust), food, or miscellaneous Pb ingestion pathways. The AALM exposure module allows the user to simulate multi-pathway exposures that are constant or that vary in time increments as small as 1 day and that occur at any age from birth to 90 years. The user can select to run a systemic biokinetics simulation based on either the Leggett (AALM-LG) or O'Flaherty (AALM-OF) biokinetics models. Parameters in both systemic models were re-calibrated with observations of blood, bone, and soft tissue Pb concentrations in children and adults (EPA 2014a). The version of the AALM described in EPA (2014a) was implemented in Advanced Continuous Simulation Language (acslX, ver. 3.1.4.2). The ICRP Human Respiratory Tract Model (HRTM) deposition and absorption parameters are used in both the AALM-LG and AALM-OF, which allows simulation of inhaled Pb particles of specified size ranges and absorption kinetics (ICRP 1994). The gastrointestinal tract model includes age-dependent absorption fractions and parameters for RBA of Pb from all ingestion pathways.

The structures of the two systemic biokinetics models in AALM-OF and AALM-LG are based on the O'Flaherty and Leggett models, respectively, with the following modifications. Growth parameters from the O'Flaherty Model are used in both models to simulate age-dependent body weight tissue weights. This provides a means for calculating tissue concentrations as the Pb mass (μg) divided by the tissue weight (g). Concentrations of Pb in bone wet weight are converted to concentration per g bone mineral by dividing the wet weight concentration by the ash fraction of bone. This conversion provides a means for comparing model predictions of bone Pb concentration with bone XRF data, which is typically reported in units of Pb per g bone mineral. Parameters for RBA of Pb in each intake medium include the

gastrointestinal tract model. This provides a means for independently adjusting the absorption fraction for each of the intake pathways (including respiratory tract-to-gastrointestinal tract) and maintains mass balance for fecal excretion of unabsorbed Pb. Inhalation, deposition, mucociliary clearance, and absorptive clearance of airborne Pb is simulated with a simplified implementation of the ICRP HRTM.

The AALM systemic biokinetic models were recalibrated from the original Leggett and O'Flaherty Models (EPA 2014b). The sequential recalibration utilized several sources of data on blood and bone Pb concentrations in humans. Parameters that control the uptake and retention of Pb in red blood cells were recalibrated using paired data on whole blood and plasma Pb concentrations in children and adults (Bergdahl et al. 1997c, 1998, 1999; Hernández-Avila et al. 1998; Manton et al. 2001; Schütz et al. 1996; Smith et al. 2002). Parameters that control plasma-to-urine clearance were recalibrated based on clearance estimates from studies that measured paired plasma concentration and urinary Pb excretion in adults (Araki et al. 1986; Chamberlain et al. 1978; Manton and Cook 1984; Manton and Malloy 1983). Autopsy data from children and adults were used to evaluate parameters that control the relationship between of tissue Pb concentrations and bone Pb concentrations (Barry 1975). The relationship between bone and plasma Pb concentrations was evaluated with paired data for plasma Pb concentration and XRF bone Pb in adults (Cake et al. 1996; Hernández-Avila et al. 1998). The long-term rate elimination of Pb from blood and bone was evaluated with data on blood and XRF bone Pb in retired Pb workers (Nilsson et al. 1991).

The calibrated AALM was evaluated with data on PbBs measured in infants (Ryu et al. 1983; Sherlock and Quinn 1986) or adults (Rabinowitz et al. 1976) who consumed known quantities of Pb. In the Ryu et al. (1983) study, PbBs were monitored in formula-fed infants who were fed measured quantiles of formula. PbBs predicted from the AALM-LG were within 1 SD of the group means and the r^2 for predictions was 0.85. Predictions from the AALM-OF were uniformly higher than observations and the r^2 for predictions was 0.76. Sherlock and Quinn (1986) measured PbB in infants at age 13 weeks and estimated dietary intake of Pb for each infant based on Pb measurements made in duplicate diet samples collected daily during week 13. The observed dose-blood Pb relationship was predicted with r^2 values of 0.95 for AALM-LG and 0.98 for AALM-OF. Rabinowitz et al. (1976) conducted a pharmacokinetics study in which four adults ingested daily doses of [^{207}Pb] nitrate for periods up to 124 days. Concentrations of ^{207}Pb in blood, urine, and feces were then monitored during and following cessation of exposure, and data on daily intakes and blood concentrations for each subject were reported. Absorption fractions for Pb were estimated for each individual based on mass balance in feces. AALM-LG

predictions are closer to the observations; r^2 values ranged from 0.92 to 0.98 for four subjects in the study. The AALM-OF predicted a slower accrual and decline of blood Pb, and lower peak PbBs ($r^2 < 0.25$).

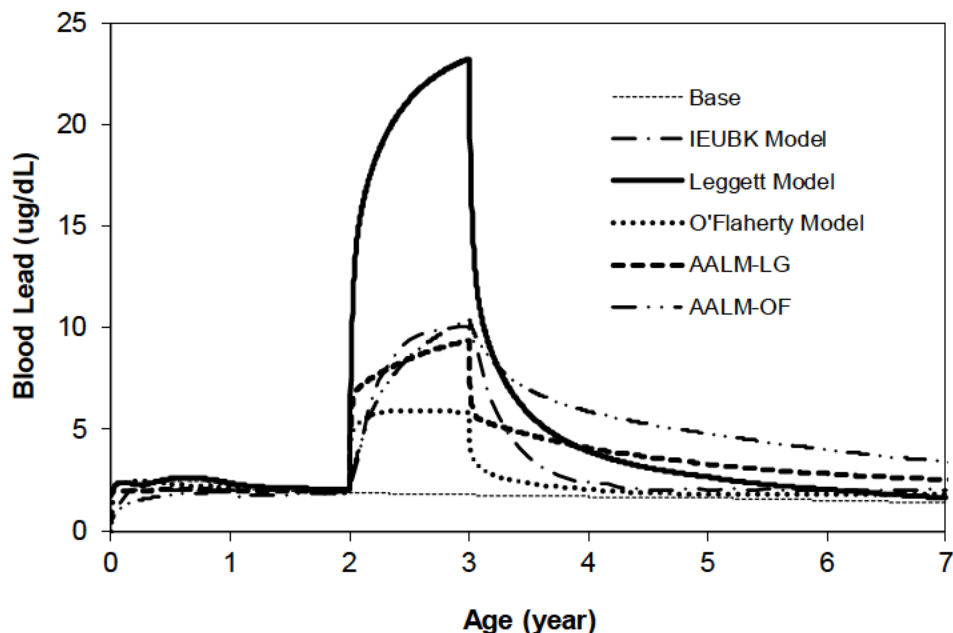
3.1.5.5 Model Comparisons

The O'Flaherty, IEUBK, and Leggett Model differ considerably in the way each represents tissues, exchanges of Pb between tissues, and Pb exposure. The AALM includes biokinetics models based on, but updated from, the O'Flaherty and Leggett models.

Figure 3-4 compares the PbBs predicted by each model for a hypothetical child who ingests 100 µg Pb/day in soil for a period of 1 year beginning at the age of 2 years (e.g., equivalent to ingestion of 100 µg soil/day at a soil Pb concentration of 1,000 mg Pb/g soil). The 100-µg/day exposure is superimposed on a baseline exposure that yields a PbB of approximately 2 µg/dL at 2 years of age. All five models predict an increase in PbB towards a quasi-steady state during the exposure period, followed by a decline towards the pre-exposure baseline PbB with an apparent half-time of approximately 1 month. Predicted PbBs at the end of the 12-month soil exposure period were 10, 23, 5.9, 9.4, and 10.4 µg/dL for the IEUBK Model, Leggett Model, O'Flaherty Model, AALM-LG, and AALM-OF, respectively. Differences in the magnitude of the predicted impact of the soil exposure on PbB reflect differences in assumptions about Pb biokinetics and cannot be attributed solely to different assumptions about Pb bioavailability.

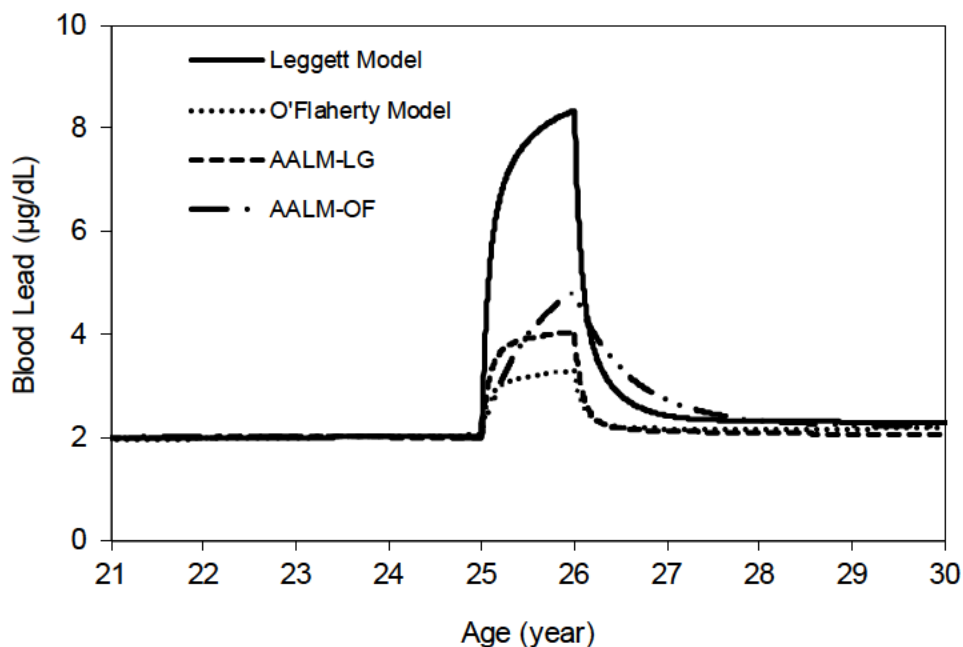
Bioavailability assumptions in the models for the age range 2–3 years are: O'Flaherty Model, 45% (50% at age 2 years, decreasing to 40% at age 3 years); IEUBK Model, 30% (soil Pb at low intakes); Leggett Model, 30%; and AALM-LG and AALM-OF 34% (38% at age 2 years and decreasing to 30% at age 3 years). A comparison of model predictions for a similar exposure during adulthood (100 µg Pb/day for 1 year, beginning at age 25) is shown in Figure 3-5. Predicted PbBs at the end of the 12-month soil exposure period were 8.4, 3.3, 4.0, and 4.8 µg/dL for the Leggett Model, O'Flaherty Model, AALM-LG, and AALM-OF, respectively. All four models predict a smaller change in PbB in adults, compared to children, for a similar increment in exposure. This is attributed, in part, to assumptions of lower Pb bioavailability in adults (i.e., O'Flaherty, 8%; Leggett, 15%; AALM-LG and AALM-OF, 8%).

Figure 3-4. Blood Lead Concentrations (PbBs) in Children Predicted by the IEUBK, Leggett, and O'Flaherty Models and AALM*



*The simulations are of a hypothetical child who has a PbB of 2 $\mu\text{g/dL}$ at age 2 years, and then experiences a 1-year exposure to 100 $\mu\text{g Pb/day}$. The 100 $\mu\text{g/day}$ exposure was simulated as an exposure to lead in soil in the IEUBK Model. Default bioavailability assumptions were applied in all three models.

Figure 3-5. Blood Lead Concentrations (PbBs) in Adults Predicted by the Leggett and O'Flaherty Models and AALM*



*The simulations are of a hypothetical adult who has a PbB of 2 $\mu\text{g/dL}$ at age 25 years, and then experiences a 1-year exposure to 100 $\mu\text{g Pb/day}$. Default bioavailability assumptions were applied in all three models.

3.1.5.6 Slope Factor Models

Slope factor models have been used as simpler alternatives to compartmental models for predicting PbBs, or the change in PbB, associated with a given exposure (Abadin et al. 1997; Bowers et al. 1994; Carlisle and Wade 1992; EPA 2017d; Maddaloni et al. 2005; Stern 1994, 1996). In slope factor models, Pb biokinetics is represented with a simple linear relationship between the PbB and either Pb uptake (biokinetic slope factor, BSF) or Pb intake (intake slope factor, ISF). The models take the general mathematical forms:

$$PbB = E \cdot ISF$$

$$PbB = E \cdot AF \cdot BSF$$

where E is an expression for exposure (e.g., soil intake x soil Pb concentration) and AF is the absorption fraction for Pb in the specific exposure medium of interest. Intake slope factors are based on ingested Pb, rather than absorbed Pb and, therefore, integrate both absorption and biokinetics into a single slope factor, whereas models that utilize a biokinetic slope factor (BSF) to account for absorption in the relationship include an absorption parameter. Slope factors used in various models are presented in Table 3-2. Of the various models presented in Table 3-2, the Bowers et al. (1994) and EPA (2017b) models implement BSFs. The slope factors used in both models (approximately 0.4 µg/dL per µg Pb/day) are similar to BSFs predicted from the O'Flaherty Model (0.65 µg/dL per µg Pb uptake/day) and Leggett Model (0.43 µg/dL per µg Pb uptake/day) for simulations of adult exposures (Maddaloni et al. 2005).

Table 3-2. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Intake route	Slope factor		Absorption fraction
			Intake	Biokinetics	
Bowers et al. 1994	Adult	Ingestion of soil/dust	ND	0.375	0.08
Carlisle and Wade 1992	Child	Ingestion of soil/dust	0.07	ND	ND
		Ingestion of water	0.04		
Carlisle and Wade 1992	Adult	Ingestion of soil/dust	0.018	ND	ND
		Ingestion of water	0.04		
Cal EPA 2017	Child	Ingestion of soil/dust	ND	0.16	0.44
		Inhalation of respirable dust	0.192	ND	ND
		Dermal contact	0.0001	ND	ND
EPA 2017d; Maddaloni et al. 2005	Adult	Ingestion of soil/dust	ND	0.4	0.12

Table 3-2. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Intake route	Slope factor		Absorption fraction
			Intake	Biokinetics	
Stern 1994	Child	Ingestion of soil/dust	T (0.056, 0.16, 0.18)	ND	ND
Stern 1996	Adult	Ingestion of soil dust	U (0.014, 0.034)	ND	ND

ND = no data; T = triangular probability distribution function (PDF); U = uniform PDF

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to Pb are discussed in Section 5.7, Populations with Potentially High Exposures.

Age. Children and the elderly are likely to have increased susceptibility to Pb compared to non-elderly adults. As reviewed in Section 3.1.2 (Distribution), Pb crosses the placenta and is distributed to the fetus; neonates are also exposed to Pb in breast milk. Epidemiological studies show that umbilical cord PbB (reflective of neonatal PbB) and PbB in infants are associated with adverse health outcomes during childhood, including decrements in neurological function (reviewed in Chapter 2). Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Children are likely to be more susceptible than adults to Pb for the following reasons:

- (1) it is generally accepted that developing systems are more susceptible than mature systems;
- (2) absorption of Pb is higher in children compared to adults (see Section 3.1.1, Absorption); and

(3) children exhibit behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity, pica behavior [the compulsive, habitual consumption of nonfood items]), proximity of breathing zone to entrained surface dust).

Regarding the elderly, it is well-established that physiological functions (e.g., renal, neurological, cardiovascular) decline with age. Thus, populations with age-related compromises in physiological function would be anticipated to be more susceptible to Pb than younger populations. Furthermore, because aging is associated with bone loss, Pb is mobilized into blood, resulting in potential increases in PbB.

Sex. As reviewed in Chapter 2, some epidemiological studies examined health outcomes in populations stratified by sex. However, studies have not demonstrated clear sex-related susceptibilities to Pb-induced toxicity for any health effect outcome. In women, pregnancy, lactation, and post-menopausal status may increase bone demineralization, mobilizing bone Pb into the blood and potentially redistributing Pb to other tissues.

Nutritional Status. As discussed in Sections 3.1 (Toxicokinetics) and 3.4 (Interactions with other Chemicals), dietary calcium and nutritional status of iron and zinc can affect absorption of Pb, potentially leading to alterations in PbB and health effects. See Sections 3.1 and 3.4 for additional details.

Pre-existing Conditions, Diseases, and Exposure to Other Substances. Because health effects associated with Pb are observed in every organ system, it is assumed that any condition or disease that compromises physiological functions could cause increased susceptibility to Pb. Examples of underlying conditions include diseases of the kidney (e.g., glomerular nephritis), neurological system (e.g., autism), hematological system (e.g., anemia, thalassemia), and cardiovascular system (e.g., hypertension, cardiac conduction disorders). Similarly, increased susceptibility to Pb would be anticipated due to use of alcohol, tobacco, or any other substance that causes deficits in physiological function.

Genetic Polymorphisms. Numerous genetic polymorphisms that may alter susceptibility to Pb through altered toxicokinetics (i.e., absorption, distribution, and retention of Pb) or toxicodynamics (e.g., effects) have been identified. The most well-studied polymorphisms are δ -ALAD and the VDR. Several other polymorphisms that may alter susceptibility to Pb have been identified, although little data are available. In addition to the references listed below, information also was obtained from a recent review by Broberg et al. 2015.

ALAD. As reviewed in Section 2.8 (Health Effects, Hematological), Pb binds to and inhibits δ -ALAD, causing decreased hemoglobin formation, measurable decreases in blood hemoglobin concentration, and anemia. δ -ALAD is the major binding site for Pb in the blood (see Section 3.1.2). As such, polymorphisms of ALAD have the potential to alter Pb toxicokinetics, and thereby alter health effects. Many studies have evaluated the potential effects of ALAD polymorphisms on Pb distribution and toxicity. Information reviewed below was obtained from the following publications: Åkesson et al. (2000); Alexander et al. (1998b); Astrin et al. (1987); Battistuzzi et al. (1981); Bellinger et al. (1994); Bergdahl et al. (1997a, 1997b); Chia et al. (2005); Chiu et al. (2013); Fang et al. (2010); Fleming et al. (1998a); Gao et al. (2010); Hsieh et al. (2000); Hu et al. (2001); Huo et al. (2014); Jaffe et al. (2000, 2001); Kim et al. (2004); Krieg et al. (2009); Lee et al. (2001); Mitra et al. (2017); Ong et al. (1990); Pagliuca et al. (1990); Pawlas et al. (2012); Petrucci et al. (1982); Sakai et al. (2000); Schwartz (1995); Schwartz et al. (1995, 1997a, 1997b, 2000a, 2000b); Scinicariello et al. (2007, 2010); Shen et al. (2001); Sithisarankul et al. (1997); Smith (1995); Suzen et al. (2003); Szymanska-Chaowska et al. (2015); Tasmin et al. (2015); Warrington et al. (2015); Weaver et al. (2008); Wetmur et al. (1991a, 1991b); Wu et al. (2003a); and Zheng et al. (2011).

The ALAD gene encodes for the heme metabolism enzyme δ -ALAD. ALAD is a polymorphic enzyme with two alleles (ALAD-1 and ALAD-2) and three genotypes (ALAD 1,1; ALAD 1,2; and ALAD 2,2). The ALAD 2,2 genotype is rare, and is found in 1% of Caucasians; in contrast, the ALAD 1,1 and ALAD 1,2 genotypes occur in 80 and 19%, respectively, of Caucasians. The ALAD 2,2 genotype occurs in <1% of Asian and African populations. A study using NHANES III data (1988–1994) reported that 15.6% of non-Hispanic whites, 2.6% non-Hispanic blacks, and 8.8% Mexican Americans carried the ALAD-2 allele (Scinicariello et al. 2010). The ALAD-2 protein has a higher binding affinity than the ALAD-1 protein for Pb. Due to this higher binding affinity, it has been proposed that ALAD-2 sequesters Pb in erythrocytes, limiting distribution of Pb to other tissues. Numerous studies have shown that ALAD-2 carriers have higher PbB than ALAD-1 carriers. Although it has been demonstrated that ALAD genotype affects the toxicokinetics of Pb, the association between adverse effects of Pb and ALAD genotype have not been definitively established.

VDR. Several studies have evaluated the potential effects of VDR polymorphisms on Pb uptake and distribution. Information reviewed below was obtained from the following publications: Ames et al. (1999); Cooper and Umbach (1996); Gundacker et al. (2009, 2010); Haynes et al. (2003); Krieg et al. (2010); Mitra et al. (2017); Morrison et al. (1992); Onalaja and Claudio (2000); Rezende et al. (2008);

Schwartz et al. (2000a, 2000b); Szymanska-Chaowska et al. (2015); Theppeang et al. (2004); and Weaver et al. (2003b).

The VDR is located in the nucleus of intestinal, renal, and bone cells. It is involved in maintaining calcium and phosphate homeostasis and regulating bone metabolism. Binding of vitamin D3 (the active form of vitamin D) to the VDR activates genes that encode for various calcium-binding proteins involved in intestinal absorption and accumulation of calcium in bone. The VDR regulates the production of calcium-binding proteins, and accounts for up to 75% of the total genetic effect on bone density. Because Pb can replace and mimic calcium, the VDR plays a critical role in the accumulation of Pb in bone. The VDR has several polymorphic forms that are defined based on restriction enzyme digestion; these include FokI with three genotypes (FF, Ff, and ff) and BsmI with three genotypes (BB, Bb, bb). The FF genotype has been associated with higher PbB and increased bone mineral density and calcium uptake. The BB genotype has been associated with higher PbB and bone Pb. However, the role of VDR polymorphisms in the Pb uptake into bone remains to be fully elucidated.

Hemochromatosis gene (HFE). Information on HFE polymorphisms was taken from the following publications: Åkesson et al. (2000); Barton et al. (1994); Fan et al. (2014); Hopkins et al. (2008); Mitra et al. (2017); Onalaja and Claudio (2000); Park et al. (2009a); Wang et al. (2007); Wright et al. (2004); and Zhang et al. (2010).

Hemochromatosis is an autosomal, recessive disease characterized by the excessive accumulation of iron in the body. In individuals with hemochromatosis, excess iron accumulates in various organs of the body and causes damage to the liver and compromises cardiovascular function. Hemochromatosis is caused by mutations of the HFE gene, which result in defects to the HFE protein. In individuals with normal HFE, HFE binds to transferrin, decreasing the gastrointestinal absorption of iron; however, in individuals with hemochromatosis, the HFE protein is not functional, leading to an increased accumulation of iron. The absorption of Pb is linked to iron status such that Pb absorption increases when iron is limited. HFE polymorphisms have been shown to enhance Pb-induced cognitive impairment (Wang et al. 2007) and the HFE H63D polymorphism appears to enhance positive associations between bone Pb and pulse pressure (Zhang et al. 2010). However, the influence of HFE variants on absorption and health effects of Pb is still being defined.

Other polymorphisms. Several other polymorphisms have been examined to evaluate potential alterations in susceptibility to adverse effects of Pb; however, little data are available. These include:

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- *Apoprotein E (APOE)*. APOE is an intracellular transporter of cholesterol and fatty acids that is synthesized by astrocytes in the brain and plays a key role in the structure of cell membranes and myelin. There are three alleles of the APOE gene: E2, E3, and E4. It has been proposed that APOE gene variants may alter susceptibility to Pb-induced changes in neurodevelopment and neurological deficits (Stewart et al. 2002; Wright et al. 2003a).
- *Dopamine receptor D4 (DRD4), Dopamine Receptor D2 (DRD2), and Dopamine Transporter (DAT1)*. Pb is associated with alterations in the dopaminergic system, which is involved in cognition and behavior. Thus, polymorphisms of DRD4, DRD2, and DAT1 may alter susceptibility to Pb-induced neurocognitive impairment (Froehlich et al. 2007; Kordas et al. 2011; Roy et al. 2011).
- *N-Methyl-D-aspartate receptors (NMDAR subunits GRIN2A and GRIN2B)*. NMDARs mediate excitatory actions of glutamate in the central nervous system, which affect learning and memory. Polymorphisms in GRIN2A and GRIN2B have been shown to be interacting factors with PbB in association between PbB and cognitive performance in children (Rooney et al. 2018).
- *Glutathione S-transferase mu 1 (GSTM1)*. Glutathione is an intracellular scavenger of oxidants and electrophiles. It is encoded by the polymorphic gene GSTM1. Genetic alterations causing a decrease in functional glutathione could result in increased oxidative damage or inflammation (Kim et al. 2007).
- *Endothelial nitric oxide synthase (eNOS)*. Nitric oxide, an endogenous signaling molecule involved in vasodilation, is produced by a family of nitric oxide synthase enzymes, including eNOS. Polymorphisms of eNOS could increase susceptibility to Pb (Barbosa et al. 2006b).
- *Metallothionein (MT)*. MT binds to and sequesters Pb. It has been proposed that polymorphisms of MT (MT1 and MT2) may affect binding of Pb to MT and lead to an increased PbB (Chen et al. 2010; Fernandes et al. 2016; Mitra et al. 2017; Yang et al. 2013b).
- *Peptide transporter 2 (PEPT2)*. Polymorphisms of PEPT2 have been associated with increased PbB in children (Sobin et al. 2009).
- *Tumor necrosis factor-alpha (TNF-α)*: TNF-α is a cell signaling protein involved in the development of inflammation. Genetic variants in TNF-α have the potential to alter susceptibility to Pb (Kim et al. 2007).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to Pb are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see <http://www.cdc.gov/exposurereport/>). If available, biomonitoring data for Pb from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by Pb are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Biomarkers of exposure in practical use today are measurements of total Pb levels in body fluids or tissues, such as blood, bone, or urine. Tetraalkyl Pb compounds may also be measured in the breath. Of these, PbB is the most widely used and is considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, PbB measurement is the screening test of choice to identify children with elevated PbBs (CDC 2012d). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface Pb contamination from the finger if proper finger cleaning is not carried out. In children, PbBs greater than the blood lead reference value identify high-risk childhood populations and geographic areas most in need of primary prevention (CDC 2012d). In 2012, the blood lead reference value was defined as 5 µg/dL (CDC 2012d). Based on an analyses of NHANES data, geometric mean PbB decreased in the United States population during the period 2009–2014 (Tsoi et al. 2016) and the percentage of children (<6 years of age) in the United States who had PbB ≥5 µg/dL in the survey period 2014–2015 decreased compared to the survey period 2009–2010 (Baertkein and Yendell 2017; McClure et al. 2016).

PbB. Measurement of PbB is the most widely used biomarker of Pb exposure. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. The blood lead reference value was set at 5 µg/dL in 2012, based on data from NHANES 2007–2008 and 2009–2010, is 5 µg/dL (CDC 2012d). Elevated PbB (e.g., >5 µg/dL) is an indication of excessive exposure in infants and children. The biological exposure index (BEI) for Pb in blood of exposed workers is 20 µg/dL (ACGIH 2018). The BEI also notes to advise “female workers of child-bearing age about the risk of delivering a child with a PbB over the current CDC reference value.” The Occupational Safety and Health Administration’s (OSHA) permissible exposure limit (PEL) for Pb (50 µg/m³ air, 8-hour time-weighted average [TWA]) was established to keep a majority of worker PbBs below 40 µg/dL (OSHA 2016a). The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for workers (50 µg/m³ air, 8-hour TWA) is established to ensure that the PbB does not exceed 60 µg/dL (NIOSH 2016b).

The extensive use of PbB as a dose metric reflects mainly the greater feasibility of incorporating PbB measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as Pb in kidney, plasma, or bone. PbB measurements have several limitations as measures of total Pb body burden. Blood comprises <2% of the total Pb burden; most of the Pb burden resides in bone (Barry 1975). Pb is eliminated from blood more rapidly than from bone (Behinaein et al. 2014; Brito et al. 2005;

Chamberlain et al. 1978; Griffin et al. 1975; Manton et al. 2001; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976; Rentschler et al. 2012); therefore, the Pb concentration in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (Graziano 1994; Lyngbye et al. 1990). Slow release of Pb from bone can contribute to blood Pb levels long after external exposure has ceased (Fleming et al. 1997; Inskip et al. 1996; Kehoe 1987; McNeill et al. 2000; O'Flaherty et al. 1982; Smith et al. 1996). The relationship between Pb intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Pb intake-PbB relationships also vary with age as a result of age-dependency of gastrointestinal absorption of Pb, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., days to weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on total Pb body burden. A single PbB determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB (CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provides supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Hu et al. 2007; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in

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trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabecular bone compared to cortical bone (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laboratories and at different times in development of the methodology used. Historically, two XRF methods have seen the most use in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 µg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 µg/g tibia bone mineral; Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Aro et al. 2000; Behinaein et al. 2014; Todd et al. 2000, 2001, 2002). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by

biological factors, such as BMI and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the result is expressed in units of $\mu\text{g Pb per g bone mineral}$. As a result, variability in bone mineral content can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults.

Tooth Pb has been considered a potential biomarker for measuring long-term exposure to Pb (e.g., years) because Pb that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Costa de Almeida et al. 2007; Ericson 2001; Fosse et al. 1995; Gomes et al. 2004; Gulson and Wilson 1994; Gulson et al. 1996; Omar et al. 2001; Rabinowitz 1995; Rabinowitz et al. 1989, 1993; Robbins et al. 2010; Steenhout and Pourtois 1987; Tvinnereim et al. 1997). Formation of enamel and primary dentin of deciduous teeth begins *in utero* and is complete prior to the time children begin to crawl. Formation of secondary dentin begins after completion of the tooth root and continues through childhood until the tooth is lost, or otherwise loses vitality. Pb in shed deciduous teeth is not uniformly distributed. Differences in Pb levels and stable isotope signatures of the enamel and dentin suggest that Pb uptake occurs differentially in enamel and dentin (Gulson 1996; Gulson and Wilson 1994). Pb in enamel is thought to reflect primarily Pb exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate Pb after eruption of the tooth; therefore, dentin Pb is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). The technique of laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) allows measurement of Pb levels in regions of dentin formed at various times during deciduous tooth formation *in utero* and after birth (Arora et al. 2014; Shepherd et al. 2016). Accumulation of Pb in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because enamel is in direct contact with the external environment, enamel Pb levels may be more influenced than dentin Pb by external Pb levels and tooth wear (Purchase and Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth Pb and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth Pb levels ranged from <3 to >12 µg/g. Dentin Pb was found to be predictive of Pb in tibia, patella, and mean bone Pb in 32 of 63 subjects at follow-up of ≤13 years (Kim et al. 1996b). The authors estimated that a 10 µg/g increase in dentin Pb levels in childhood was predictive of a 1 µg/g increase in tibia Pb levels, a 5 µg/g increase in patella Pb levels, and a 3 µg/g increase in mean bone Pb among the young adults. Arora et al. (2014) found that Pb levels in primary (prenatal) dentin were more strongly correlated with PbBs at birth (correlation coefficient, $r=0.69$, $n=27$), whereas Pb levels in secondary (postnatal) dentin were more strongly correlated with CBLI ($r=0.38$, $n=75$). Shepherd et al. (2016) combined LA-ICP-MS with histological determinations of dentin age to reconstruct the history of incorporation of environmental Pb from various sources.

Plasma Pb Concentration. The concentration of Pb in plasma (e.g., approximately 0.04 µg/dL at PbB of 10 µg/dL) is extremely difficult to measure accurately because levels in plasma are near the quantitation limits of most analytical techniques (Bergdahl and Skerfving 1997; Bergdahl et al. 1997a) and because hemolysis that occurs with typical analytical practices can contribute to substantial measurement error (Bergdahl et al. 1998, 2006; Cavalleri et al. 1978; Smith et al. 1998a). ICP-MS offers sensitivity sufficient for measurements of Pb in plasma (Schütz et al. 1996). The technique has been applied to assessing Pb exposures in adults (Barbosa et al. 2006a; Cake et al. 1996; Hernandez-Avila et al. 1998; Manton et al. 2001; Smith et al. 2002; Tellez-Rojo et al. 2004; Tian et al. 2013). A direct comparison of Pb concentrations in plasma and serum yielded similar results (Bergdahl et al. 2006); however, the interchangeability of plasma and serum Pb measurements for biomonitoring of Pb exposure or body burden had not been thoroughly evaluated in large numbers of subjects (Bergdahl et al. 2006; Manton et al. 2001; Smith et al. 2002).

Urinary Pb. Measurements of urinary Pb levels have been used to assess Pb exposure (e.g., Chiang et al. 2008; Fels et al. 1998; Fukui et al. 1999; Gerhardsson et al. 1992; Lilis et al. 1968; Lin et al. 2001; Mendy et al. 2012; Mortada et al. 2001; Navas-Acien et al. 2005; Rentschler et al. 2012; Roels et al. 1994; Sun et al. 2008b). However, like PbB, urinary Pb excretion mainly reflects recent exposure and thus shares many of the same limitations for assessing Pb body burden or long-term exposure (Sakai 2000; Skerfving 1988). Although collection of urine is noninvasive, urine Pb levels exhibit variability with PbB, and interpretation of urine Pb levels requires estimates of GFR and measurement of urine volume (NTP 2012). A significant, but relatively weak correlation between urinary Pb levels (µg/g creatinine) and individual Pb intakes (µg/day) was observed in a study of 10–12-year-old children (β : 0.053, $R=0.320$,

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p=0.02, N=57; Chiang et al. 2008). In this study, urine sampling and measurements used to estimate intake were separated by as long as 6 months for some children, which may have contributed to the relatively weak correlation. The measurement is further complicated by variability in urine volume, which can affect concentrations independent of excretion rate (Diamond 1988) and the potential effects of decrements in kidney function on excretion, in association with high, nephrotoxic Pb exposures or kidney disease (Lilis et al. 1968; Wedeen et al. 1975). Urinary Pb concentration increases exponentially with PbB and can exhibit relatively high intra-individual variability, even at similar PbBs (Gulson et al. 1998a; Skerfving et al. 1985). However, the relationship between plasma Pb and urinary Pb ($\mu\text{g Pb/g creatinine}$) was linear in a small group of children (Rentschler et al. 2012). The linear relationship between plasma and urinary Pb may reflect the importance of plasma Pb in determining the rate of glomerular filtration and renal tubular transport of Pb (see Section 3.1.4). Urinary diethyl Pb has been proposed as a qualitative marker of exposure to tetraethyl Pb (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

The measurement of Pb excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (*EDTA provocation*), or oral dosing with dimercaptosuccinic acid (DMSA) has been used to detect elevated body burden of Pb in adults (Biagini et al. 1977; Lee et al. 2009; Lilis et al. 1968; Lin et al. 2003, 2006a, 2006b; Schwartz et al. 2000a, 2000c; Wedeen 1992; Wedeen et al. 1975) and children (Chisolm et al. 1976; Markowitz and Rosen 1981). However, the American College of Medical Toxicology (ACMT 2010) position statement on post-chelator challenge urinary metal testing states that “post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning.” The assay is not a substitute for PbB measurements in the clinical setting. Note that children whose PbBs are $\geq 45 \mu\text{g/dL}$ should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 2002a, 2012e). For additional information on recommended actions based on PbB level in children and adults, see Section 3.5 (Methods for Reducing Toxic Effects). Further limitations for routine use of the test are that EDTA must be given parenterally and requires timed urine collections. A study conducted in rats found that intraperitoneal administration of a single dose of EDTA following 3–4-month exposures to Pb in drinking water increased levels of Pb in the liver and brain (Cory-Slechta et al. 1987) raising concern for similar effects in humans who undergo the EDTA provocation test. The use of EDTA to assess bone stores of Pb (Wedeen 1992) is largely being supplanted by more direct, noninvasive procedures for measuring Pb in bone. DMSA is a Pb chelating agent that can be administered orally.

DMSA-chelatable Pb has been used as marker of Pb body burden in adults (Schwartz et al. 1997b, 2000a, 2000c; Scinicariello et al. 2007; Weaver et al. 2003a, 2003b).

Pb in Saliva and Sweat. Pb is excreted in human saliva and sweat (Genuis et al. 2011; Lilley et al. 1988; Omokhodion and Crockford 1991; Rabinowitz et al. 1976; Stauber and Florence 1988; Sears et al. 2012; Stauber et al. 1994). Sweat has not been widely adopted for monitoring Pb exposures. Lilley et al. (1988) found that Pb concentrations in sweat were elevated in Pb workers; however, sweat and PbBs were poorly correlated. This may reflect excretion of Pb in or on the skin that had not been absorbed into blood. Studies conducted in rats have found relatively strong correlations between Pb concentrations in plasma and saliva (e.g., $r^2 > 0.9$), compared to blood Pb and saliva; therefore, saliva may serve as a better predictor of plasma Pb than PbB (Timchalk et al. 2006). However, studies of saliva Pb conducted in humans have had mixed results, with some studies showing relatively strong correlations between salivary Pb concentration and PbB (Brodeur et al. 1983; Omokhodion and Crockford 1991; P'an 1981), and other studies showing weak or inconsistent relationships (Barbosa et al. 2006c; Costa de Almeida et al. 2009, 2010, 2011; Nriagu et al. 2006). Variable outcomes from these studies may reflect differences in PbBs, exposure history and/or dental health (i.e., transfer of Pb between dentin and saliva), and methods used for determining Pb in saliva. Other complicating factors reported in the literature include uncontrolled variation in salivary flow rates (Barbosa et al. 2005; Esteban and Castano 2009) and potential blood contamination of saliva (Koh and Koh 2007).

Hair and Nail Pb. Pb is incorporated into human hair and hair roots (Bos et al. 1985; Rabinowitz et al. 1976) and has been explored as a possibly noninvasive approach for estimating Pb body burden (Gerhardsson et al. 1995b; Wilhelm et al. 1989). The method is subject to error from contamination of the surface with environmental Pb and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and is a relatively poor predictor of PbB, particularly at low concentrations ($< 12 \mu\text{g/dL}$) (Campbell and Toribara 2001; Drasch et al. 1997; Esteban et al. 1999; Rodrigues et al. 2008). Nevertheless, levels of Pb in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996). Pb in hair was correlated with liver and kidney Pb in a study of deceased smelter workers (Gerhardsson et al. 1995b). Correlations between maternal and infant hair Pb concentrations have been observed (Kordas et al. 2010). Although hair Pb measurements have been used in some epidemiologic studies (Bao et al. 2009; Huel et al. 2008; Marcus et al. 2010; Shah et al. 2011), an empirical basis for interpreting hair Pb measurements in terms of body burden or exposure has not been firmly established. Nail Pb has also been utilized as a marker of Pb exposure, although nails may be contaminated with Pb from external sources (Barbosa et al. 2005; Gerhardsson et al. 1995b).

Semen Pb. Pb concentrations in semen have been explored as an internal exposure biomarker for adverse effects of Pb on the testes (Hernandez-Ochoa et al. 2005; Kasperczyk et al. 2015; Slivkova et al. 2009; Taha et al. 2013; Wu et al. 2012). Correlations between concentrations of Pb in semen and blood have been reported and vary in strength across studies (Alexander et al. 1998a, 1998b; Farias et al. 2005; Hernandez-Ochoa et al. 2005; Mendiola et al. 2011; Telisman et al. 2000). This variation may relate, in part, to analytical challenges in the measurement of the relatively low concentrations of Pb in semen. Using ICP-MS and rigorous collection methods to avoid contamination, Farias et al. (2005) reported a detection limit of 0.2 µg/L semen. Mean semen Pb concentration in a group of 160 men (age range 19–48 years) who were not exposed to Pb occupationally was 2.66 µg/L (range 0.08–19.42) and was significantly correlated with PbB (mean 10.8 µg/dL, range 4.5–40.2) and tibia bone Pb (mean 14.51 µg/g, range not-detected–44.71 µg/g).

Stable Pb Isotopes. Analysis of the relative abundance of stable isotopes of Pb in blood and other accessible body fluids (e.g., breast milk, urine) has been used to differentiate exposures from multiple sources (Flegal and Smith 1995). Relative abundances of stable isotopes of Pb (^{204}Pb , ^{206}Pb , ^{207}Pb , and ^{208}Pb) in Pb ores vary with the age of the ore (which determines the extent to which the parent isotopes have undergone radioactive decay to stable Pb). Humans have Pb isotope abundance profiles that reflect the profiles of Pb deposits to which they have been exposed. Pb isotope studies can be used to exclude sources of Pb contributing to exposure. Similarly, if exposure abruptly changes to a Pb source having a different isotope abundance profile, the kinetics of the change in profile in the person can be measured, reflecting the kinetics of uptake and distribution of Pb from the new source (Gulson et al. 2003; Maddaloni et al. 1998; Manton et al. 2003). Numerous examples of the application of stable isotope abundance measurements for studying sources of Pb exposures have been reported (Angle et al. 1995; Graziano et al. 1996; Gulson and Wilson 1994; Gulson et al. 1996, 1997b, 1999c, 2016; Manton 1977, 1998).

Effect Biomarkers Used to Assess Exposure to Pb. Certain physiological changes that are associated with Pb exposure have been used as biomarkers of exposure (see Section 3.3.2). These include measurements of biomarkers of impaired heme biosynthesis (blood zinc protoporphyrin, urinary coproporphyrin, erythrocyte ALAD activity, serum ALA). These types of measurements have largely been supplanted with measurement of PbB for the purpose of assessing Pb exposure due to the higher sensitivity of PbB measurements in quantifying lower level Pb exposures.

3.3.2 Biomarkers of Effect

Certain effects of Pb have been used in diagnosing Pb poisoning to support measurements of PbB; however, none of these diagnostic aids are considered preferable to measurement of PbB. A multisite study of populations living near four NPL sites was conducted to assess the relationship between exposure (PbB and area of residence) and biomarkers of four organ systems: immune system dysfunction, kidney dysfunction, liver dysfunction, and hematopoietic dysfunction (ATSDR 1995). The geometric mean PbB in those living in the target areas was 4.26 µg/dL (n=1,645) compared with 3.45 µg/dL for a group living in comparison areas (n=493). In children <6 years old, the corresponding means were 5.37 versus 3.96 µg/dL. In subjects ≥15 years old, the target and comparison values were 3.06 and 3.63 µg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbBs <10 µg/dL. Pb in soil and water was found to be higher in comparison areas than in the target areas, but Pb in house dust and in interior paint was higher in the target areas. PbB correlated with Pb in soil and dust, but not with Pb in paint and water. Multivariate regression analyses showed that of all the biomarkers analyzed, PbB was significantly associated with, and predictive of, hematocrit in adults ≥15 years of age and with increased mean serum IgA in children 6–71 months of age. The biological significance of these associations is unclear since both hematocrit and IgA levels were well within normal ranges and were hardly different than levels in subjects from the comparison areas.

Pb inhibits heme biosynthesis, which is necessary for production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is not specific for Pb (Bernard and Becker 1988). However, inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as zinc-protoporphyrin (ZPP). This fraction is preferentially measured by hematofluorometers. Extraction methods measure all of the protoporphyrin present, but strip the zinc from the ZPP during the extraction process. For this reason, extraction results are sometimes referred to as (zinc) free erythrocyte protoporphyrin (FEP). Although the chemical forms measured by the two methods differ slightly, on a weight basis, they are roughly equivalent; thus, results reported as EP, ZPP, or FEP all reflect essentially the same analyte. An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average Pb levels at the site of erythropoiesis over the previous 4 months (Janin et al. 1985). The concentration of EP rises above background at PbBs of 25–30 µg/dL, above which, there is a positive correlation between PbB and EP (CDC 1985; Gennart et al. 1992a; Roels and Lauwerys 1987; Soldin et al. 2003; Wildt et al. 1987). Pb toxicity is generally considered to be present when a PbB ≥10 µg/dL is associated with an EP level ≥35 µg/dL (CDC 1991; Somashekaraiah et al.

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1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986a; Moore and Goldberg 1985). Similarly, elevated EP can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). Conversely, since EP does not go up until the PbB exceeds 25 µg/dL, and the blood lead reference value was set at 5 µg/dL in 2012, relying on EP measures would result in many false negative cases. Some have estimated that relying only on ZPP screening to predict future Pb toxicity would miss approximately three cases with toxic PbBs in every 200 workers at risk (Froom et al. 1998). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of photochemical decomposition; thus, assay samples must be protected from light. However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990).

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of Pb effect (Graziano 1994; Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). ALAD activity is negatively correlated with PbBs of 5–95 µg/dL, with >50% inhibition occurring at PbBs >20 µg/dL (Hernberg et al. 1970; Morita et al. 1997; Roels and Lauwerys 1987). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbBs between 21 and 30 µg/dL (Schuhmacher et al. 1997). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected when PbB exceeds 35 µg/dL in adults and 25–75 µg/dL in children (NAS 1972; Roels and Lauwerys 1987; Sakai and Morita 1996; Schuhmacher et al. 1997).

Another potential biomarker for hematologic effects of Pb is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975, 1977). Pb can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975, 1977). Furthermore, since basophilic stippling is not universally found in chronic Pb poisoning, it is relatively insensitive to lesser degrees of Pb toxicity (CDC 1985). The activity of adenine dinucleotide synthetase (NADS) in

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erythrocytes has also been explored as a biomarker for predicting PbBs >40 µg/dL; NADS activity is negatively correlated with PbB over the range 5–80 µg/dL (Morita et al. 1997).

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased Pb absorption or Pb concentrations in the blood (Rosen et al. 1980). Pb inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986a; Landrigan 1989). Children with PbBs of 12–120 µg/dL showed decreased serum 1,25-dihydroxyvitamin D concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for Pb exposure and several diseases can influence this measurement.

One of the most sensitive systems affected by Pb exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes than adults. In children, encephalopathy has been associated with PbBs as low as 70 µg/dL (CDC 1985). An early sign of peripheral manifestations of neurotoxicity is gastrointestinal colic, which can occur with PbBs above 50 µg/dL. The most sensitive peripheral index of neurotoxicity of Pb is reported to be slowed conduction velocity in small motor fibers of the ulnar nerve in workers with PbBs of 30–40 µg/dL (Landrigan 1989). Other potential biomarkers of Pb suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory function tests (Williamson and Teo 1986). However, these tests are not specific to elevated Pb exposure.

Functional deficits associated with Pb-induced nephrotoxicity increase in severity with increasing PbB. Effects include decreased glomerular filtration, enzymuria and proteinuria, and impaired transport function. Biomarkers for these changes include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β₂µ-globulin, α₁µ-globulin, retinol binding protein). However, none of these markers are specific for Pb-induced nephrotoxicity. A characteristic histologic feature of Pb nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Interactions between Pb and other chemicals can be classified into two categories: interactions with contaminants that are commonly found together with Pb at hazardous waste sites, and interactions with essential elements (ATSDR 2004a, 2004b, 2006; EPA 2014c).

Interactions with Other Contaminants. Several metals and metalloids frequently are found together with Pb at hazardous waste sites, including arsenic (As), cadmium (Cd), manganese (Mn), zinc (Zn), copper (Cu), and inorganic mercury (Hg). ATSDR (2004a, 2004b, 2006) has conducted assessments to predict interactions of these chemicals with Pb; conclusions are presented in Table 3-3. For each co-contaminant, interactions were classified as less than additive (indicating an antagonistic effect with Pb), additive (indicating no effect of combined exposure), or greater than additive (indicating a synergistic effect with Pb). Greater-than-additive effects were observed for neurological effects for As and Cd, male reproductive effects for Cd, and renal effects for Hg. Interactions for other metals were either less than additive or additive for cardiovascular (Cd, Zn), developmental (Zn), hematological (As, Cd, Mn, Zn, Cu), immunological (Cd), neurological effects (Zn), renal (As, Cd, Mn, Zn, Cu), and male reproductive (Zn) effects. Other metals that may interact with Pb include selenium and chromium(VI) (Nordberg et al. 2015). Observed interactions of metals and metalloids with Pb could be the results of alterations to Pb toxicokinetics, toxicodynamics, or a combination of both.

Table 3-3. Influence of Other Metals and Metalloids on Lead (Pb) Toxicity

Organ system	Metal					
	Arsenic ^a	Cadmium ^a	Manganese ^b	Zinc ^b	Copper ^b	Inorganic mercury ^c
Cardiovascular	–	< or 0	–	<	–	–
Developmental	–	–	–	<	–	–
Hematological	< or 0	< or 0	0	< or 0	<	–
Immunological	–	<	–	–	–	–
Neurological	>	>	–	< or 0	<	–
Renal	0	< or 0	0	<	–	>
Male reproductive	–	>	–	<	–	–

^aATSDR 2004a.

^bATSDR 2004b.

^cATSDR 2006.

< = less than additive; 0 = additive (no effect); > = greater than additive; – = not assessed

Interactions with Essential Elements. In physiological systems, Pb mimics divalent cations (calcium, iron, zinc). Substitution of Pb for essential elements in membrane transport systems is the mechanism by which Pb is absorbed from the intestine and crosses cell membranes throughout the body. Thus, numerous interactions between Pb and essential elements have been observed, including the following (additional details on these finding are provided in Section 3.1, Toxicokinetics):

- Dietary calcium intake appears to affect Pb absorption. An inverse relationship has been observed between dietary calcium intake and PbBs in children (Elias et al. 2007; Mahaffey et al. 1986; Schell et al. 2004; Ziegler et al. 1978).
- Nutritional iron status may affect Pb absorption in children. Higher PbBs have been observed in iron-deficient children compared to children who are iron replete. This observation suggests that iron deficiency may result in higher absorption of Pb or, possibly, other changes in Pb biokinetics that would contribute to higher PbBs (Mahaffey and Annest 1986; Marcus and Schwartz 1987).
- In young children (ages 6–12 months), PbB increased in association with lower dietary Zn levels (Schell et al. 2004). It is not clear, however, if these associations were caused by changes in Pb absorption.

3.5 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to Pb. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to Pb. When specific exposures have occurred, poison control centers, medical toxicologists, or other clinicians with expertise and experience treating and managing Pb-exposed adults and/or children should be consulted. The following resources provide specific information about treatment and management of patients following exposure to Pb:

AAP. 2005. Lead exposure in children: Prevention, detection, and management. *Pediatrics* 116(4):1036-1046. 10.1542/peds.2005-1947.

AAP. 2016. Council on Environmental Health. Prevention of childhood lead toxicity. *Pediatrics* 38(1):e20161493

ATSDR. 2017. Case studies in environmental medicine (CSEM). Lead toxicity. https://www.atsdr.cdc.gov/csem/lead/docs/csem-lead_toxicity_508.pdf. August 30, 2018.

Calello DP, Henretig FM. 2014. Lead. In: Goldfrank's toxicologic emergencies. Tenth ed. New York, NY: McGraw-Hill, 1219-1234.

Holland MG, Cawthon D. 2016. ACOEM Position Statement. Workplace lead exposure. *J Occup Environ Med* 58(12):e371-e374.

Leikin JB, Paloucek FP. 2008. Lead. In: Poisoning and toxicology handbook. Fourth ed. Boca Raton, FL: CRC Press, 807-811.

CDC. 2002a. Managing elevated blood levels among young children. Recommendations from the Advisory Committee on Childhood Lead Poisoning. Centers for Disease Control and Prevention. <https://www.cdc.gov/nceh/lead/casemanagement/managingEBLLs.pdf>. July 18, 2018.

Kosnett MJ. 2001. Lead. In: Ford M, Delaney KA, Ling L, et al., eds. Clinical toxicology. St. Louis: WB Saunders, 723-736.

Kosnett MJ. 2005. Lead. In: Brent J, Wallace KL, Burkhart KK, et al., eds. Critical care toxicology. Philadelphia, PA: Elsevier Mosby, 821-836.

PEHSU. 2013. Recommendations on medical management of childhood lead exposure and poisoning. Pediatric Environmental Health Specialty Units.

Additional publicly available clinical resources for the health care professional can be found in Appendix D.

3.5.1 Reducing Absorption Following Exposure

No treatment modalities to reduce Pb absorption have been developed. Therefore, the most important intervention is to identify and remove the source of exposure (AAP 2005, 2016; ATSDR 2017; CDC 2012e). Pb absorption from the gastrointestinal tract is influenced by nutrition, especially calcium, iron, and vitamin C (AAP 2005; CDC 2012e). It is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of Pb and that children eat regular meals since more Pb is absorbed on an empty stomach (AAP 2005; CDC 2002a, 2012e). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of Pb following acute exposure include the following (AAP 2016; ATSDR 2017; Calello and Henretig 2014; Kosnett et al. 2007):

- remove the individual from the source of exposure;
- mitigate source of exposure;
- if suspected that elevated PbB is due to ingestion of a foreign object (e.g., Pb paint chips, toys or jewelry containing Pb, Pb ammunition), radiographic imaging is suggested;
- if elevated PbB is due to ingestion of a foreign object, decontamination of the bowel (surgical or gastric lavage) is indicated; and
- ensure that diet is adequate in calcium, iron, and vitamin C.

For children, specific recommended actions based on PbB levels are summarized in Table 3-4. CDC considers PbB to be elevated in children when it exceeds a reference value defined as the 97.5th percentile for the U.S. population. In 2012, CDC adopted a blood lead reference value, based on data from NHANES 2007–2008 and 2009–2010, of 5 µg/dL (CDC 2016).

Table 3-4. Recommended Actions Based on Child Blood Lead Level (PbB)

PbB (µg/dL)	Recommended actions
<Reference value ^a	<ul style="list-style-type: none"> • Routine assessment of nutritional and developmental milestones • Education on common sources of Pb exposure • Follow-up PbB monitoring
5-19	<ul style="list-style-type: none"> • Follow recommendations for <Reference value • Nutritional counseling for calcium and iron intake
20-44	<ul style="list-style-type: none"> • Complete history and physical examination with neurodevelopmental assessment • Environmental assessment of home and lead hazard reduction • Follow-up PbB monitoring • Assess iron status, hemoglobin, and hematocrit • Abdominal x-ray and bowel decontamination if indicated
≥45 and ≤69	<ul style="list-style-type: none"> • Follow recommendations for 45–69 µg/dL • Complete neurological examination • Consider oral chelation therapy with consultation with a medical toxicologist or pediatric environmental health expert or unit • Consider hospitalization if cannot assure mitigation of Pb source
≥70	<ul style="list-style-type: none"> • Hospitalize • Initiate chelation therapy with consultation with a medical toxicologist or pediatric environmental health expert or unit • Follow recommendations for ≥45 and ≤69 µg/dL • Environmental investigation of the home and lead hazard reduction; child receiving chelation therapy should not return to home until lead hazard remediation is completed

^a5 µg/dL (CDC 2012d).

Source: CDC 2012f

For occupational exposures, OSHA and NIOSH have developed recommendations to reduce Pb exposure through procedures and surveillance. In 1987, NIOSH created the Adult Blood Lead Epidemiology and Surveillance (ABLES) program to monitor adult PbBs through coordinated efforts with state agencies (NIOSH 2017a). This program was designed to decrease the rate of adults with PbBs ≥10 µg/dL as a result of work-related Pb exposure. In 2015, NIOSH designated PbB of 5 µg/dL as the PbB reference value and defined elevated PbB as PbB ≥5 µg/dL (NIOSH 2017a). Several federal and state agencies work together to reduce the rate of elevated PbBs among workers. The OSHA (1995) mandated rule on

Pb provides recommendations to reduce occupational Pb exposure for general industry, shipyard employment, and construction through use of respirators, protective clothing, routine biological monitoring of PbB and zinc protoporphyrin, and medical assessments for workers with elevated PbB. More recently, Holland and Cawthon (2016) suggested the actions based on PbB levels, with a baseline PbB <5 µg/dL (Table 3-5).

Table 3-5. Recommended Actions for Workers Based on Blood Lead Level (PbB)

PbB (µg/dL)	Recommended actions
All workers	<ul style="list-style-type: none"> PbB monitoring at initial employment Monitor PbB every 6 months after initial employment monitoring PbB goal is <5 µg/dL for pregnant workers
≥5–9	<ul style="list-style-type: none"> Increase monitoring if indicated Recommend removal for pregnant workers or workers who are trying to become pregnant; return to work may be considered if two consecutive PbB measurements are <5 µg/dL Continue PbB monitoring as noted above
10–19	<ul style="list-style-type: none"> Monitor PbB every 2 months until two consecutive PbB measurements are <10 µg/dL Mandatory medical removal for pregnant workers or workers who are trying to become pregnant; return to work may be considered if two consecutive PbB measurements are <5 µg/dL Continue PbB monitoring as noted above Evaluate exposure, controls, and work practices
≥20	<ul style="list-style-type: none"> Remove from work if repeat PbB measurement in 4 weeks is ≥20 µg/dL or if single PbB measurement is ≥30 µg/dL Monitor PbB monthly; return to work after two consecutive monthly PbB measurements are <15 µg/dL Continue PbB monitoring as noted above Evaluate exposure, controls, and work practices
≥30	<ul style="list-style-type: none"> Removed from exposure immediately Monitor PbB monthly; return to work after two consecutive monthly PbB measurements are <15 µg/dL Continue PbB monitoring as noted above Evaluate exposure, controls, and work practices

Source: Holland and Cawthon (2016)

3.5.2 Reducing Body Burden

Pb is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of Pb is found in bones, respectively. Pb may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

Currently available methods to obviate the toxic effects of Pb are based on their ability to reduce the body burden of Pb by chelation. All of the chelating agents bind inorganic Pb, enhance its excretion, and facilitate the transfer of Pb from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated Pb via the kidney, caution should be used when treating a patient with renal failure. For all cases where chelation therapy is considered or implemented, medical providers should consult with a medical toxicologist or an expert in the medical management of Pb toxicity (CDC 2002a, 2012e). Chelation treatment should be administered in conjunction with meticulous supportive therapy (Calello and Henretig 2014). Most of the information below regarding chelators was obtained from Calello and Henretig (2014) and Kosnett (2005, 2007).

Several pharmacological substances are available for chelation therapy for Pb intoxication. Chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), $\text{CaNa}_2\text{-EDTA}$ (or EDTA), and 2,3-dimercaptosuccinic acid (DMSA; Succimer[®]). Dosages and administration protocols for these agents vary with patient age, PbB level, and symptom types and severity. Specific treatment protocols should be developed in consultation with clinical experts in the management of Pb toxicity for the most current chelation therapy procedures for children and adults (CDC 2002a, 2012e).

Dimercaprol (BAL). The mechanism of action of BAL is through formation of stable chelate-metal compounds intra- and extracellularly. BAL is administered parenterally. The onset of action for BAL is 30 minutes. BAL increases fecal excretion of Pb as chelated Pb is excreted predominantly in bile within 4–6 hours; BAL also increases urinary excretion of chelated Pb. A number of adverse reactions have been associated with BAL, including nausea, vomiting, hypertension, tachycardia, headache, increased secretions, anxiety, abdominal pain, and fever.

CaNa₂-EDTA (or EDTA). EDTA works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of Pb 20–50 times. EDTA is administered parenterally. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage.

2,3-Dimercaptosuccinic acid (DMSA; Succimer®). The mechanism of action of DMSA is similar to BAL. DMSA is administered orally. DMSA has been shown to be as effective as EDTA in increasing the urinary excretion of Pb. Minimal adverse effects that have been reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on calcium, iron, magnesium, and copper.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Pb is a naturally occurring element with an abundance of 0.0016% in the earth's crust (Davidson et al. 2014). It is a member of Group 14 (IVA) of the periodic table. Natural Pb is a mixture of four stable isotopes: ^{204}Pb (1.4%), ^{206}Pb (24.1%), ^{207}Pb (22.1%), and ^{208}Pb (52.4%). The Pb isotopes ^{206}Pb , ^{207}Pb , and ^{208}Pb are the stable decay product of the naturally occurring decay series of uranium, actinium, and thorium, respectively (Haynes 2014).

Pb is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world (King et al. 2014). Its properties, such as corrosion resistance, density, and low melting point, make it a familiar metal in pipes, solder, weights, and storage batteries. The chemical identities of Pb and several of its compounds are provided in Table 4-1.

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead	Lead(II) acetate	Lead(II) azide	Lead(II) bromide
Synonym(s) and registered trade name(s)	C.I. 77575; C.I. Pigment metal 4; Glover; Lead flake; Lead S2; Omaha; Omaha & Grant; SI; SO ^a	Acetic acid lead(2+) salt (2:1); neutral lead acetate; plumbous acetate; normal lead acetate; sugar of lead; salt of Saturn ^b	Lead azide ^b	Lead bromide (PbBr ₂); plumbous bromide ^b
Chemical formula	Pb ^b	Pb(CH ₃ CO ₂) ₂ ^b	Pb(N ₃) ₂ ^b	PbBr ₂ ^b
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7439-92-1 ^b	301-04-2 ^b	13424-46-9 ^b	10031-22-8 ^b

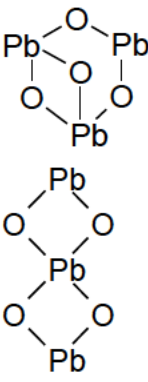
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Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead(II) chloride	Lead(II) chromate	Lead(II) tetrafluoroborate ^c	Lead(II) iodide
Synonym(s) and registered trade name(s)	Lead chloride (PbCl ₂); Lead(2+) chloride; Plumbous chloride ^b	Chromic acid (H ₂ CrO ₄ lead(2+) salt (1:1); Chrome yellow; Cologne yellow; King's yellow; Leipzig yellow; Paris yellow; C.I. Pigment Yellow 34; lead chromium oxide (PbCrO ₄); plumbous chromate; C.I. 77600 ^b	Tetrafluoro borate(1-) Lead(2+) ^a	Lead iodide (PbI ₂); Plumbous iodide ^b
Chemical formula	PbCl ₂ ^b	PbCrO ₄ ^b	Pb(BF ₄) ₂ ^a	PbI ₂ ^b
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7758-95-4 ^b	7758-97-6 ^b	13814-96-5 ^a	10101-63-0 ^b

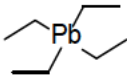
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Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead molybdenum chromate	Lead(II) nitrate	Lead(II) oxide	Lead(II,II,IV) oxide
Synonym(s) and registered trade name(s)	Chromic acid, lead and molybdenum salt; chromic acid lead salt with lead molybdate; C.I. Pigment Red 104; Lead chromate, Molybdenum-Lead chromate; Molybdenum Orange ^a	Nitric acid lead(2+) salt (2:1); Plumbous nitrate ^b	C.I. 77577; C.I. Pigment Yellow 46; Lead oxide; Lead oxide yellow; Lead protoxide; Litharge; Litharge Yellow L-28; Massicot; Massicotite; Plumbous oxide; Yellow lead ochre ^a	Lead tetraoxide; Lead tetroxide; Lead oxide red; C.I. Pigment Red 105; C.I. 77578; Gold satinobre; Lead orthoplumbate; Lead oxide (3:4); Mineral Orange; Mineral Red; Paris Red; Saturn Red; Minium; Plumboplumbic oxide; Red Lead; Red Lead oxide; Trilead tetraoxide ^{d,e}
Chemical formula	No data	Pb(NO ₃) ₂ ^b	PbO ^a	Pb ₃ O ₄ ^e
Chemical structure	Not applicable	Not applicable	Not applicable	
CAS Registry Number	12709-98-7 ^a	10099-74-8 ^b	1317-36-8 ^a	1314-41-6 ^d

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Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead(II) phosphate	Lead(II) styphnate	Lead(II) sulfate
Synonym(s) and registered trade name(s)	C.I. 77622; Lead orthophosphate; Lead phosphate (3:2); Lead(2+) phosphate; normal lead orthophosphate; Phosphoric acid, lead(2+) salt (2:3); Plumbous phosphate; Trilead phosphate ^a	Lead trinitroresorcinate ^f	Anglesite; C.I. 77630; C.I. Pigment White 3; Fast White; Freemans White Lead; Lead bottoms; Milk white; Mulhouse White; Sulfuric acid, lead(2+) salt (1:1) ^a
Chemical formula	Pb ₃ (PO ₄) ₂ ^a	Pb(C ₆ H ₃ N ₃ O ₈) ₂ ^f	PbSO ₄ ^b
Chemical structure	Not applicable	Not applicable	Not applicable
CAS Registry Number	7446-27-7 ^a	15245-44-0 ^f	7446-14-2 ^b
Characteristic	Lead(II) sulfide	Tetraethyl lead	Lead(II) carbonate
Synonym(s) and registered trade name(s)	C.I. 77640; Galena; Natural lead sulfide; Plumbous sulfide ^a	Tetraethylplumbane; Lead tetraethyl; TEL ^b	Carbonic acid, lead(2+) salt (1:1); Cerussite; Dibasic lead carbonate; Lead(2+) carbonate; White lead ^a
Chemical formula	PbS ^a	Pb(C ₂ H ₅) ₄ ^a	PbCO ₃ ^a
Chemical structure	Not applicable		Not applicable
CAS Registry Number	1314-87-0 ^a	78-00-2 ^b	598-63-0 ^a

^aLewis 2012.^bO'Neil et al. 2013.^cStable only in aqueous solution (Haynes 2014).^dNLM 2020.^eHaynes 2014.^fBoileau et al. 2012.

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Pb, a blueish-white metal with bright luster, is very soft, highly malleable, ductile, a poor conductor of electricity, and is very resistant to corrosion (Haynes 2014). A clean Pb surface will not be attacked by dry air; however, in moist air, the surface will react and become coated with a layer of lead(II) oxide (PbO). This coating may be hydrated and combine with carbon dioxide to form lead(II) carbonate (PbCO₃) (Carr et al. 2004). This protective coating of insoluble Pb compounds slows or halts corrosion of the underlying metal. Pb is rarely found in its metallic form in nature and commonly occurs as a

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mineral with sulfur or oxygen. The most important Pb mineral is galena (PbS). Other common Pb-containing minerals include anglesite (PbSO₄), cerussite (PbCO₃), and minium (Pb₃O₄) (Carr et al. 2004; Davidson et al. 2014; Haynes 2014).

Pb can exist in the 0 oxidation state in metallic Pb and in compounds as the +2 or +4 oxidation states. In the environment, Pb is primarily found in the +2 state in inorganic compounds. The chemistry of inorganic Pb compounds is generally similar to that of the Group 2(II) or alkaline earth metals. There are three common oxides of Pb: lead(II) oxide (PbO); lead(II,IV) oxide or lead tetroxide (Pb₃O₄); and lead(IV) oxide or lead dioxide (PbO₂). The +4 state is only formed under strongly oxidizing conditions. Inorganic Pb(+4) compounds are relatively unstable and would not be expected to be found under ordinary environmental conditions. Pb is amphoteric, meaning that it can react with acids and bases. In acid, Pb forms Pb(+2) (plumbous) and Pb(+4) (plumbic) salts and in basic solution, it forms plumbites (PbO₂²⁻) and plumbates (Pb(OH)₆²⁻) (Carr et al. 2004). In organolead compounds, Pb is typically in the tetravalent (+4) oxidation state (Carr et al. 2004; Haynes 2014).

Data on the physical and chemical properties of Pb and several of its compounds are provided in Table 4-2.

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Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead	Lead(II) acetate	Lead(II) azide	Lead(II) bromide
Molecular weight	207.2 ^a	325.3 ^b	291.24 ^a	367.0 ^b
Color	Bluish-white, silvery, gray metal ^a	White crystals ^b	Needles or white powder ^a	White orthorhombic crystals ^b
Physical state	Solid	Solid	Solid	Solid
Melting point	327.4°C ^a	280°C ^b	Decomposes at 190°C ^c	371°C ^b
Boiling point	1,740°C ^a	Decomposes ^b	No data	892°C ^b
Density	11.34 g/cm ³ at 20°C ^a	3.25 g/cm ^{3b}	4.17 g/cm ³ at 20°C ^c	6.69 g/cm ^{3b}
Odor	No data	Slightly acetic odor (trihydrate) ^a	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble ^d	443,000 mg/L at 20°C ^b	230 mg/L at 18°C ^a	9,750 mg/L at 25°C ^b
Acids	Soluble in dilute nitric acid ^d ; reacts with sulfuric acid ^a	Soluble in acid ^e	Freely soluble in acetic acid ^a	No data
Bases	No data	Soluble in alkali ^e	No data	No data
Organic solvents	Soluble in glycerin; slightly soluble in alcohol ^e	Slightly soluble in alcohol; freely soluble in glycerol ^d	No data	Insoluble in alcohol ^b
Partition coefficients:				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	1.77 mmHg at 1,000°C ^a	No data	No data	0.0075 mmHg at 374°C ^b
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant ^f	Not relevant ^f	Not relevant ^f	Not relevant ^f
Explosive limits	No data	No data	Explodes at 350°C ^a	No data
Valence state	0	+2	+2	+2

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) chloride	Lead(II) chromate	Lead(II) tetrafluoroborate	Lead iodide
Molecular weight	278.1 ^g	323.19 ^a	380.8 ^b	461.05 ^g
Color	White, orthorhombic needles ^g	Yellow or orange-yellow powder ^a	No data	Yellow hexagonal crystals ^g
Physical state	Solid	Solid	Stable only in aqueous solution ^b	Solid
Melting point	501°C ^g	844°C ^a	No data	402°C ^g
Boiling point	950°C ^g	No data	No data	954°C ^g
Density	5.85 g/cm ^{3g}	6.12 g/cm ^{3b}	No data	6.16 g/cm ^{3g}
Odor	No data	No data	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	9,900 mg/L at 20°C ^g	0.2 mg/L ^a	Soluble ^b	630 mg/L at 20°C ^g
Acids	Slightly soluble in dilute hydrochloric acid ^g	Soluble in dilute nitric acid; insoluble in acetic acid ^a	No data	No data
Bases	Slightly soluble in dilute ammonia ^g	No data	No data	No data
Organic solvents	Insoluble in alcohol ^g	No data	No data	Insoluble in alcohol ^g
Partition coefficients:				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	7.5 mmHg at 637°C ^b	No data	No data	0.75 mmHg at 470°C ^b
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant ^f	Not relevant ^f	Not relevant ^f	Not relevant ^f
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead molybdenum chromate	Lead(II) nitrate	Lead(II) oxide	Lead(II,II,IV) oxide
Molecular weight	No data	331.23 ^g	223.21 ^g	685.57 ^e
Color	No data	Cubic or monoclinic colorless crystals ^g	Reddish-yellow; yellow (above 489°C) ^g	Bright red heavy powder ^a ; red tetrahedral crystals ^b
Physical state	No data	Solid	Solid	Solid
Melting point	No data	Begins to decompose above 205°C ^g	897°C (begins to sublime before melting) ^g	830°C ^b ; 500°C ^e
Boiling point	No data	No data	Decomposes at 1,472°C ^g	Decomposes between 500-530°C ^d
Density	No data	4.53 g/cm ^{3g}	9.53 g/cm ³ (Litharge) ^g ; 9.6 g/cm ³ (Massicot) ^g	8.92 g/cm ^{3b} ; 9.1 g/cm ^{3e}
Odor	No data	No data	No data	No data
Odor threshold:	No data	No data	No data	No data
Solubility:				
Water	No data	56.5 g/100 mL at 20°C ^g	50.4 mg/L at 25°C (Litharge) ^g ; 106.5 mg/L at 25°C (Massicot) ^g	Insoluble in water ^d
Acid	No data	Insoluble in concentrated nitric acid ^a	Soluble ^g	Dissolves in acetic acid or hot hydrochloric acid ^{b,g}
Base	No data	Soluble in alkali and ammonia ^g	Soluble ^g	No data
Organic solvents	No data	87.7 mg/L (43% aqueous ethanol) at 22°C ^g	Insoluble in alcohol ^a	Insoluble in alcohol ^g
Partition coefficients:				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	0.0075 mmHg at 724°C ^b	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	Not relevant ^f	Not relevant ^f	Not relevant ^f	Not relevant ^f
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2, +2, +4

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Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) phosphate	Lead(II) styphnate	Lead(II) sulfate
Molecular weight	811.54 ^a	450.29 ^h	303.25 ^g
Color	White powder ^a	Monoclinic orange-yellow crystal (monohydrate) ^b	White, heavy, crystalline powder ^a
Physical state	Solid	Solid	Solid
Melting point	1,014°C ^a	No data	1,170°C ^g
Boiling point	No data	No data	No data
Density	6.9 g/cm ^{3a}	3.1 g/cm ³ (monohydrate); 2.9 g/cm ³ (anhydrous) ^b	6.2 g/cm ^{3g}
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water	Insoluble ^b	Insoluble ^b	42.5 mg/L at 25°C ^g
Acid	Soluble in nitric acid ^a	No data	Soluble in concentrated acids ^g
Base	Soluble in fixed alkali hydroxides ^a	No data	Soluble in alkalies ^g
Organic solvents	Insoluble in alcohol ^a	No data	Insoluble in alcohol ^a
Partition coefficients:			
Log K _{ow}	No data	No data	No data
Log K _{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	Not relevant ^f	Not relevant ^f	Not relevant ^f
Explosive limits	No data	Detonates at 260°C ^b	No data
Valence state	+2	+2	+2

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead(II) sulfide	Tetraethyl lead	Lead(II) carbonate
Molecular weight	239.25 ^g	323.45 ^a	267.22 ^g
Color	Metallic black cubic crystals ^g	Colorless ^a	Colorless rhombic crystals ^g
Physical state	Solid	Liquid ^a	Solid
Melting point	1,114°C ^d	No data	315°C (decomposes) ^g
Boiling point	Sublimes at 1,281°C ^d	200 °C; 227.7°C (with decomposition) ^a	No data
Density	7.57–7.59 g/cm ^{3g}	1.653 g/cm ^{3a}	6.6 g/cm ^{3g}
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water	124.4 mg/L 20°C ^g	0.29 mg/L ⁱ	1.1 mg/L at 20°C ^g
Acid	Soluble in nitric acid ^g	No data	Soluble ^g
Base	Insoluble in alkalies ^d	No data	Soluble in alkalies; insoluble in ammonia ^g
Organic solvents	Insoluble in alcohol ^a	Soluble in benzene, petroleum ether, gasoline; slightly soluble in alcohol ^a	Insoluble in alcohol ^g
Partition coefficients:			
Log K _{ow}	No data	4.15 ^j	No data
Log K _{oc}	No data	No data	No data
Vapor pressure	0.0075 mmHg at 705°C ^b	0.26 mmHg at 25°C ⁱ	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	200°F (93°C) (closed cup) ^k	No data
Flammability limits	No data	Lower flammable limit: 1.8% by volume ^k	No data
Conversion factors	Not relevant ^f	No data	Not relevant ^f
Explosive limits	No data	No data	No data
Valence state	+2	+4	+2

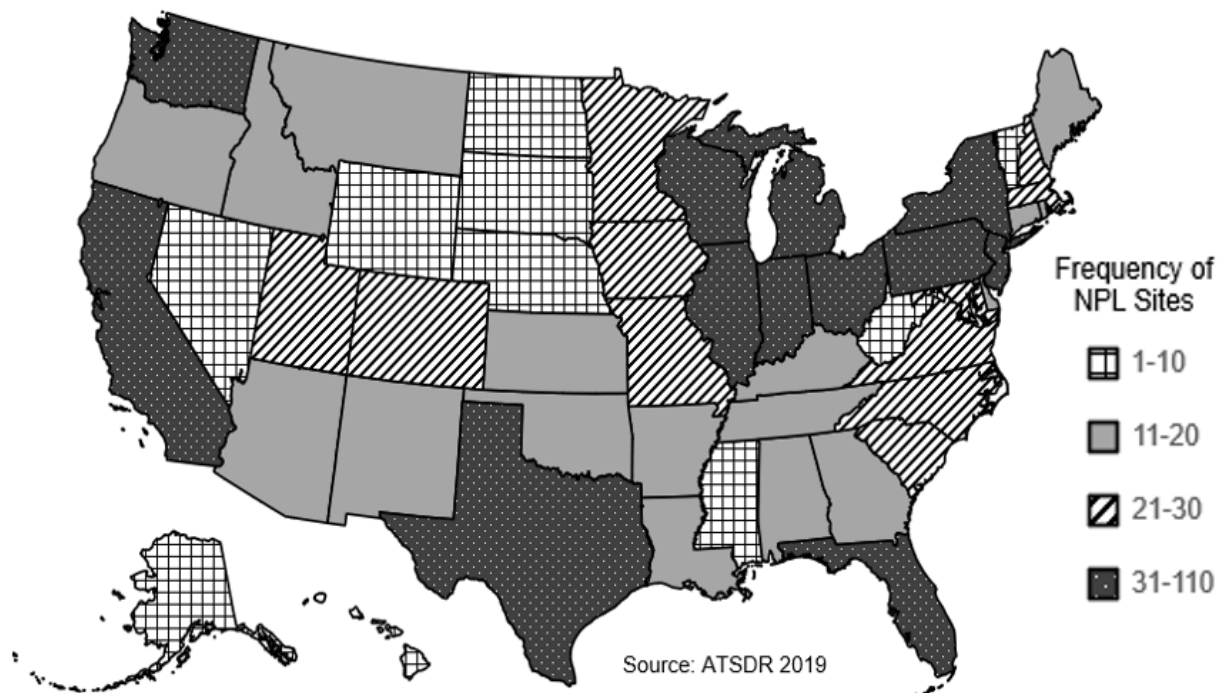
^aO'Neil et al. 2013.^bHaynes 2014.^cAkhavan 2004.^dLarrañaga et al. 2016.^eJacob 2012.^fSince these compounds exist in the atmosphere in the particulate state, their concentrations are expressed as µg/m³ only.^gCarr et al. 2004.^hMolecular weight calculated from atomic weights.ⁱFeldhake and Stevens 1963.^jWang et al. 1996.^kNFPA 2002.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Pb and Pb compounds have been identified in at least 1,287 and 46 sites, respectively, of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites evaluated for Pb is not known. The number of sites in each state is shown in Figures 5-1 and 5-2, respectively. Of these 1,287 sites for Pb, 1,273 are located within the United States, 2 are located in the Virgin Islands, 2 are located in Guam, and 10 are located in Puerto Rico (not shown). All the sites for Pb compounds are only in the United States.

Figure 5-1. Number of NPL Sites with Lead Contamination



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Other conditions that increase Pb mobility in soils are reducing conditions (low redox potential; for example, anoxia) and high chloride content.

Pb is dispersed throughout the environment primarily as the result of anthropogenic activities. In the air, Pb is in the form of particles and is removed by rain or gravitational settling. The solubility of Pb compounds in water is a function of pH, ionic strength, and the presence of humic material. Solubility is highest in acidic water. Soil and sediment are an important sink for Pb. Because Pb is strongly adsorbed to soil, very little is transported through runoff to surface water or leached to groundwater except under acidic conditions. Anthropogenic sources of Pb include the mining and smelting of ore, manufacture and use of Pb-containing products, combustion of coal and oil, and waste incineration. Many anthropogenic sources of Pb, most notably leaded gasoline, Pb-based paint, Pb solder in food cans, Pb-arsenate pesticides, and shot and sinkers, have been eliminated or are regulated. Pb compounds released to the environment may be transformed to other Pb compounds; however, Pb is an element and cannot be destroyed or degraded. Because Pb does not degrade over time, deposits of Pb in the environment by current and former uses leave their legacy as higher concentrations of Pb in the environment. These deposits can continue to be a source for potential Pb exposure (e.g., soil particles containing Pb also may be resuspended and redeposited). Plants and animals may bioconcentrate Pb, but Pb is not biomagnified in the aquatic or terrestrial food chain.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Segments of the general population at highest risk of health effects from Pb exposure are preschool-age children and pregnant women and their fetuses. Other segments of the general population with an increased exposure include individuals living near sites where Pb was produced or disposed. Some of the more important Pb exposures have occurred as a result of living in urban environments, particularly in areas near stationary emission sources (e.g., smelters); renovation of homes containing Pb-based paint; pica (the compulsive, habitual consumption of nonfood items); contact with interior Pb paint dust; occupational exposure; and secondary occupational exposure (e.g., families of workers in Pb industries). Higher exposures may also occur to residents living in close proximity to NPL sites that contain elevated levels of Pb.

The primary source of Pb in the environment has historically been anthropogenic emissions to the atmosphere. In 1984, combustion of leaded gasoline was responsible for approximately 90% of all anthropogenic Pb emissions. The United States gradually phased out the use of Pb alkyls in gasoline, and by 1990, auto emissions accounted for only 33% of the annual Pb emissions (EPA 1996b). Use of Pb

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additives in most motor fuels was totally banned after December 31, 1995 (EPA 1996a). The ban went into effect on February 2, 1996. The ban did not include off-road vehicles, including aircraft, racing cars, farm equipment, and marine engines. Pb additives are still used in fuels for piston driven airplane engines and it continues to be commercially available for other off-road uses. Atmospheric deposition is the largest source of Pb found in soils. Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb particles are removed from the atmosphere primarily by wet and dry deposition. The average residence time in the atmosphere is 10 days. Over this time, long-distance transport, up to thousands of kilometers, may take place. The speciation of Pb in these media varies widely depending upon such factors as temperature, pH, and the presence of humic materials. Pb is largely associated with suspended solids and sediments in aquatic systems, and it occurs in relatively immobile forms in soil.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

The most important mineable Pb ore is galena (PbS), which is commonly associated with other minerals, typically zinc ores. Anglesite (PbSO₄) and cerussite (PbCO₃), formed by the weathering of galena, are two other important Pb minerals. Pb is processed from ore to refined metal in four steps: ore dressing; smelting; drossing; and refining. Ore dressing involves crushing, grinding, and beneficiation (concentration) (King et al. 2014).

Since 1998, U.S. production of Pb has shifted to the domestic secondary Pb industry (USGS 2014). Since 2014, primary Pb metal has not been produced in the United States (USGS 2016). The Doe Run Resources Corporation operated the last domestic primary Pb smelter-refinery facility in the United States at Herculaneum, Missouri and it was closed at the end of 2013. Pb-acid batteries are the dominant source of recoverable Pb scrap, accounting for nearly 100% of all secondary Pb (USGS 2016, 2019).

Domestic mines produced 368,000 metric tons of recoverable Pb in 2014, a more than 11% increase from 2013. Nearly all of the secondary Pb produced in 2014 was by 7 companies operating 12 plants in Alabama, California, Florida, Indiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas (USGS 2016). Secondary (recycled) Pb, derived from mainly scrapped Pb-acid batteries, accounted for all of the domestic refined Pb production in 2014. Due to plant closings, U.S. production

of secondary refined Pb decreased in 2014 by 11% to 1.02 metric tons, from 1.5 metric tons in 2013 (USGS 2016).

World mine production of Pb was 4.91 million metric tons in 2014, a decrease of 9% from 2013. The United States accounted for approximately 8% of global mine production in 2014. The United States ranked third in global mine production behind China and Australia, which accounted for 49 and 15%, respectively. World production of refined Pb (primary and secondary) was 10.6 million metric tons in 2014. China produced about 45% of global refined Pb in 2014 with the United States as the second leading world producer of refined Pb, accounting for 10% (USGS 2016). In 2017 and 2018 worldwide mine production of Pb was reported as 4.58 and 4.40 million metric tons, respectively (USGS 2019). As in previous years, China was the dominant producer accounting for nearly half of the world production.

Manufacturers and importers of Pb metal and selected Pb compounds are listed in Table 5-1. These data are from EPA’s Chemical Data Access Tool (now called Chemical Data Reporting [CDR]), which provides information on chemicals submitted to the EPA under the Toxic Substance Control Act that are manufactured or imported into the United States. Manufacturing volumes for more recent years are not available in the CDR as most manufacturers have withheld these data as confidential business information; however, as in previous years, the U.S. Geological Survey (USGS) reported total Pb mined in the United States in its Minerals Commodity summaries and these data for 2015–2018 are provided in Table 5-2. According to the USGS, five Pb mines located in the state of Missouri along with five mines in Alaska, Idaho, and the state of Washington accounted for all domestic Pb mine production (USGS 2019).

Table 5-1. U.S. Manufacturers of Lead Metal and Selected Lead Compounds

Company	Location	Domestic manufacturing (pounds/year)
Lead		
5n Plus Inc.	Fairfield, Connecticut	36,671
Colfin Specialty Steel Corp.	New Brighton, Pennsylvania	2,552
Compliance Administrators & Project Services Inc.	Bloomington, California	848,008
Concorde/Interspace Battery	West Covina, California	348,998
Doe Run Co.	Herculaneum, Missouri	280,000,000
East Penn Manufacturing Co. Inc.	Lyon Station, Pennsylvania	194,537,569
Exide Technologies	Bristol, Tennessee	150,000

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Table 5-1. U.S. Manufacturers of Lead Metal and Selected Lead Compounds

Company	Location	Domestic manufacturing (pounds/year)
	Columbus, Georgia	4,200,000
	Forest City, Missouri	84,000,000
	Fort Smith, Arkansas	3,600,000
	Frisco, Texas	140,000,000
	Kansas City, Kansas	9,100,000
	Los Angeles, California	230,000,000
	Manchester, Iowa	16,000,000
	Muncie, Indiana	160,000,000
	Reading, Pennsylvania	130,000,000
	Salina, Kansas	990,000
Gopher Resource	Eagan, Minnesota	310,000,000
	Tampa, Florida	38,000,000
Horsehead Holding Corp.	Chicago, Illinois	2,444,492
	Palmerton, Pennsylvania	3,867,016
	Rockwood, Tennessee	1,872,054
	Snelling, South Carolina	2,012,236
Johnson Controls	Canby, Oregon	36,832,250
	Geneva, Illinois	47,025,828
	Holland, Ohio	82,721,150
	Kernersville, North Carolina	204,679,893
	Middletown, Delaware	86,732,852
	Tampa, Florida	3,069,380
	Yuma, Arizona	359,977,380
Johnson Controls Distribution Center	Saint Joseph, Missouri	2,550,177
	St. Joseph, Missouri	266,151,342
Renco Group Inc.	Boss, Missouri	310,000,000
Sanders Lead Co., Inc.	Troy, Alabama	471,954,520
Stemar Investments Inc.	Butler, Pennsylvania	40,506
Yuasa Battery Inc.	Laureldale, Pennsylvania	1,492,754
Lead(II) nitrate		
American Pacific Corp.	Cedar City, Utah	42,500
Lead(II) oxide		
C&D Technologies Inc.	Attica, Indiana	18,657,255
	Leola, Pennsylvania	1,348,311
	Milwaukee, Wisconsin	48,491,557
Crown Battery Manufacturing Co.	Fremont, Ohio	25,600,000

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Table 5-1. U.S. Manufacturers of Lead Metal and Selected Lead Compounds

Company	Location	Domestic manufacturing (pounds/year)
Fiamm Energy LLC	Waynesboro, Georgia	4,700,000
Hammond Group Inc.	Hammond, Indiana	3,585,529
	Pottstown, Pennsylvania	8,287,521
Renco Group Inc.	Boss, Missouri	7,700,000
Steel Dust Recycling	Millport, Alabama	2,000,000
Superior Battery Manufacturing	Russell Springs, Kentucky	16,866,793
Trojan Battery Co.	Lithonia, Georgia	38,540,700
	Santa Fe Springs, California	35,241,500
Lead(II) styphnate		
Alliant Techsystems Inc.	Lewiston, Idaho	78,767
Alliant Techsystems Operations LLC	Independence, Missouri	43,489
Lead(II) sulfate		
Crown Battery Manufacturing Co.	Fremont, Ohio	768,000
East Penn Manufacturing Co., Inc.	Corydon, Iowa	17,006,710
	Lyon Station, Pennsylvania	220,436,420
Johnson Controls	Canby, Oregon	6,098,880
	Geneva, Illinois	11,340,306
	Holland, Ohio	10,714,048
	Middletown, Delaware	5,749,910
	Tampa, Florida	5,506,240
	Yuma, Arizona	86,756
Johnson Controls Distribution Center	Saint Joseph, Missouri	306,021
	St. Joseph, Missouri	29,577,055
Palos Verdes Bldg Corp.	Augusta, Georgia	6,904,629
Superior Battery Manufacturing	Russell Springs, Kentucky	22,905,105
Trojan Battery Co.	Lithonia, Georgia	58,127,100
	Santa Fe Springs, California	53,083,500
Lead(II) chloride		
Horsehead Holding Corp.	Monaca, Pennsylvania	1,891,700
	Palmerton, Pennsylvania	11,484,955

Source: EPA 2014d

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-2. U.S. Lead Production 2015–2018

	Production volumes in metric tons			
	2015	2016	2017	2018
Mine, lead in concentrates	370,000	346,000	310,000	260,000
Secondary refinery, old scrap	1,050,000	986,000	1,130,000	1,300,000

Source: USGS 2019

Tables 5-3 (Pb) and 5-4 (Pb compounds) list the facilities in each state that manufacture or process Pb or Pb compounds, the intended use, and the range of maximum amounts of Pb that are stored on site. The data listed in Tables 5-3 and 5-4 are derived from the Toxics Release Inventory (TRI) (TRI18 2020). The data presented in Table 5-3 are for Pb metal and the data from Table 5-4 are for all Pb compounds. Facilities with ≥ 10 full-time employees in certain TRI-covered industry sectors (e.g., manufacturing) must submit data on releases and other waste management for TRI-listed chemicals (Pb and Pb compounds are TRI listed). Therefore, there are sources for Pb and Pb compounds not contained in the TRI database. In comparing TRI data with that of previous years, it is important to note that starting in 2001, the threshold for reporting Pb and all Pb compounds was reduced to 100 pounds, except for Pb contained in a stainless steel, brass, or bronze alloy. Previously, reporting was only required of facilities that manufactured or processed $>25,000$ pounds annually or that used $>10,000$ pounds annually. Beginning in 1998, additional industries were required to report, including metal mining, coal mining, electrical utilities, and Resource Conservation and Recovery Act (RCRA)/Solvent Recovery. Table 5-3 lists the producers of primary Pb metal and selected Pb compounds. Companies listed are those producing Pb compounds in commercial quantities $>5,000$ pounds or \$10,000 in value annually. Table 5-4 shows the U.S. production volumes for Pb for 2010 through 2013. During this time, the primary Pb production declined, while secondary Pb production was relatively constant.

Table 5-3. Facilities that Produce, Process, or Use Lead

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	4	100	99,999	12
AL	105	0	999,999,999	1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	67	0	49,999,999	1, 2, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	52	0	9,999,999	1, 3, 5, 7, 8, 9, 10, 11, 12, 14
CA	188	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	33	0	99,999	1, 5, 6, 7, 8, 10, 11, 12, 14

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Table 5-3. Facilities that Produce, Process, or Use Lead

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
CT	42	0	99,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DC	6	0	9,999	1, 7, 8, 11, 12, 13, 14
DE	6	0	99,999	7, 12, 14
FL	223	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	108	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	1	0	99	1, 5
HI	2	0	99,999	8, 12
IA	114	0	9,999,999	1, 2, 5, 6, 7, 8, 9, 11, 12, 13, 14
ID	27	0	49,999,999	1, 2, 3, 5, 8, 9, 11, 12, 13, 14
IL	228	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
IN	161	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	70	0	9,999,999	1, 3, 5, 7, 8, 9, 10, 12, 13, 14
KY	79	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	46	0	999,999	1, 2, 3, 5, 8, 9, 10, 11, 12, 13, 14
MA	55	0	999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	35	0	99,999	1, 5, 7, 8, 9, 10, 11, 12, 14
ME	20	0	99,999	1, 2, 3, 4, 5, 8, 9, 11, 12, 13, 14
MI	148	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
MN	123	0	99,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	92	0	9,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	62	0	999,999	1, 5, 7, 8, 9, 10, 12, 14
MT	15	0	99,999	1, 2, 5, 11, 12, 13, 14
NC	162	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14
ND	14	0	9,999	1, 5, 8, 9, 12, 14
NE	62	0	999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13, 14
NH	30	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
NJ	43	0	99,999	1, 2, 5, 7, 8, 9, 11, 12, 13, 14
NM	17	0	999,999	1, 5, 6, 8, 9, 10, 11, 12, 14
NV	28	0	999,999	1, 2, 4, 5, 8, 9, 12, 13, 14
NY	140	0	999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
OH	237	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	54	0	999,999	1, 2, 3, 5, 7, 8, 11, 12, 14
OR	48	0	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
PA	182	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	5	100	9,999	2, 3, 8, 9, 12
RI	15	0	999,999	1, 5, 7, 8, 9, 10, 11, 12, 13, 14
SC	81	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	14	0	99,999	1, 2, 5, 7, 8, 9, 13, 14

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-3. Facilities that Produce, Process, or Use Lead

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
TN	110	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	326	0	49,999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	50	0	999,999	1, 5, 6, 8, 9, 10, 11, 12, 13, 14
VA	98	0	999,999	1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14
VI	3	0	99	7, 9, 14
VT	11	0	99,999	1, 2, 3, 5, 8, 11, 12, 13, 14
WA	57	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
WI	165	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	31	0	999,999	1, 2, 5, 8, 9, 10, 11, 12, 13, 14
WY	12	0	99,999	1, 5, 6, 8, 9, 10, 11, 12, 13, 14

^aPost office state abbreviations used.^bAmounts on site reported by facilities in each state.^cActivities/Uses:

- | | | |
|----------------------|-----------------------------|--------------------------|
| 1. Produce | 6. Reactant | 11. Manufacture Aid |
| 2. Import | 7. Formulation Component | 12. Ancillary |
| 3. Used Processing | 8. Article Component | 13. Manufacture Impurity |
| 4. Sale/Distribution | 9. Repackaging | 14. Process Impurity |
| 5. Byproduct | 10. Chemical Processing Aid | |

Source: TRI18 2020 (Data are from 2018)

Table 5-4. Facilities that Produce, Process, or Use Lead Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	16	0	499,999,999	1, 5, 9, 12, 13, 14
AL	130	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	68	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	65	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
CA	315	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	76	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
CT	39	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DC	1	100	999	14
DE	5	100	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
FL	150	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
GA	108	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
GU	3	0	99	1, 5, 7, 9, 12, 13, 14
HI	14	0	99,999	1, 2, 5, 7, 9, 12, 13, 14
IA	66	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-4. Facilities that Produce, Process, or Use Lead Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
ID	31	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 11, 12, 13, 14
IL	166	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	151	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	40	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	64	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	85	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	53	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	35	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
ME	13	0	999,999	1, 2, 4, 5, 8, 9, 12, 13, 14
MI	102	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	50	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	74	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MP	1	0	99	1, 5, 12, 13, 14
MS	50	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14
MT	20	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
NC	149	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	20	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
NE	24	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
NH	14	0	999,999	1, 2, 5, 7, 8, 9, 11, 12, 14
NJ	55	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
NM	18	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NV	51	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	82	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	175	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	81	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	55	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	195	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	11	0	99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 14
RI	19	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
SC	101	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	11	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
TN	89	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
TX	330	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	41	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	84	0	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VI	2	0	99	1, 5, 12, 0
VT	5	0	9,999	7, 8, 14
WA	76	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-4. Facilities that Produce, Process, or Use Lead Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
WI	100	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	44	0	49,999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
WY	16	0	999,999	1, 2, 3, 4, 5, 8, 9, 12, 13, 14

^aPost office state abbreviations used.^bAmounts on site reported by facilities in each state.^cActivities/Uses:

- | | | |
|----------------------|-----------------------------|--------------------------|
| 1. Produce | 6. Reactant | 11. Manufacture Aid |
| 2. Import | 7. Formulation Component | 12. Ancillary |
| 3. Used Processing | 8. Article Component | 13. Manufacture Impurity |
| 4. Sale/Distribution | 9. Repackaging | 14. Process Impurity |
| 5. Byproduct | 10. Chemical Processing Aid | |

Source: TRI18 2020 (Data are from 2018)

5.2.2 Import/Export

In 2014, 1,080 and 593,000 metric tons of Pb as base bullion and pigs and bars, respectively, were imported into the United States. Imports have increased since 2010 when 602 and 271,000 metric tons of Pb as base bullion and pigs and bars, respectively, were imported. In 2014, 65,100 metric tons, Pb content of Pb pigments and compounds were imported in the United States (USGS 2016). In 2015, 2016, 2017, and 2018 imports of Pb refined metal (unwrought) were reported as 521,000, 533,000, 658,000, and 580,000 metric tons, respectively (USGS 2019).

Exports of Pb in ore and concentrates and Pb materials, excluding scrap were 299,000 and 83,500 metric tons, respectively, in 2010 as compared to 365,000 and 61,300 metric tons, respectively, in 2014. In 2013 and 2014, 34,900 and 36,400 metric tons of Pb scrap were exported, respectively (USGS 2016). Total exports of Pb (Pb in concentrates and refined metal, unwrought gross weight) were reported as 406,000, 384,000, 293,000, and 324,000 metric tons in 2015, 2016, 2017, and 2018, respectively (USGS 2019).

5.2.3 Use

Pb may be used in the form of metal, either pure or alloyed with other metals, or as chemical compounds. The main uses of Pb and its compounds are in Pb-acid batteries, with most other applications using Pb alloys. The commercial importance of Pb is based on its physical properties, including its low melting

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point, ease of casting, high density, softness, malleability, low strength, ease of fabrication, acid resistance, electrochemical reaction with sulfuric acid, and chemical stability in air, water, and soil (King et al. 2014).

In the United States in 2014, Pb was consumed by over 70 companies to manufacture products such as ammunition; building-construction materials; covering for power and communication cable; Pb-acid storage batteries; Pb oxides for ceramics, chemicals, glass, and pigments; Pb sheet; and solder for construction, electronic components and accessories, metal containers, and motor vehicles (USGS 2016). In 2018, it was estimated that the Pb-acid battery industry accounted for >85% of the domestic consumption of Pb in the United States (USGS 2019). Pb-acid batteries were primarily used as starting-lighting-ignition (SLI) batteries for automobiles and trucks and as industrial-type batteries for standby power for computer and telecommunications networks and for motive power. Global consumption of refined Pb was 11.71 million metric tons in 2018, (USGS 2019).

Prior to the EPA beginning to regulate the Pb content in gasoline during the early 1970s, approximately 250,000 tons of organic Pb (e.g., tetraethyl Pb) were added to gasoline on an annual basis in the United States (Giddings 1973). These Pb-based “anti-knock” additives increased the octane rating of the gasoline and, as a result, increased engine efficiency (Giddings 1973). In 1971, the average Pb content for a gallon of gasoline purchased in the United States was 2.2 g/gallon (Giddings 1973). After determining that Pb additives would impair the performance of emission control systems installed on motor vehicles, and that Pb particle emission from motor vehicles presented a significant health risk to urban populations, EPA, in 1973, initiated a phase-down program designed to minimize the amount of Pb in gasoline over time. By 1988, the phase-down program had reduced the total Pb usage in gasoline to <1% of the amount of Pb used in the peak year of 1970 (EPA 1996a).

In 1990, a Congressional amendment to the Clean Air Act (CAA) banned the use of gasoline containing Pb or Pb additives as fuel in most motor vehicles. On February 2, 1996, the EPA incorporated the statutory ban in a direct final rule, which defined unleaded gasoline as gasoline containing trace amounts of Pb up to 0.05 g/gallon (EPA 1996a). The definition still allowed trace amounts of Pb, but expressly prohibited the use of any Pb additive in the production of unleaded gasoline. The term “lead additive” was defined to include pure Pb as well as Pb compounds (EPA 1996a). Although the regulatory action of Congress banned the use of leaded gasoline as fuel in motor vehicles, it did not restrict other potential uses of gasoline containing Pb or Pb additives (EPA 1996a). Gasoline produced with Pb additives continues to be made and marketed for use as fuels in aircraft, race cars, and non-road engines such as

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farm equipment engines and marine engines to the extent allowed by law (EPA 1996a), but tetraethyl Pb has not been produced in the United States since March 1991. All gasoline sold for motor vehicle use since January 1, 1996 has been unleaded (EPA 2020a).

Table 5-5 lists the uses of the specific Pb compounds identified in Chapter 4.

Table 5-5. Current and Former Uses of Selected Lead Compounds

Compound	Uses
Lead(II) acetate	Dyeing of textiles, waterproofing, varnishes, lead driers, chrome pigments, gold cyanidation process, insecticide, anti-fouling paints, analytical reagent, hair dye
Lead(II) azide	Primary detonating compound for high explosives, firing of Pb-based ammunition
Lead(II) bromide	Photopolymerization catalyst, inorganic filler in fire-retardant plastics, general purpose welding flux
Lead(II) carbonate	Polymerization catalyst, component of high pressure lubricating greases, coating on vinyl chloride polymers
Lead(II) chloride	Preparation of lead salts, lead chromate pigments, analytical reagent
Lead(II) chromate	Pigment in industrial paints, rubber, plastics, ceramic coatings; organic analysis
Lead(II) tetrafluoroborate	Salt for electroplating lead; can be mixed with stannous fluoborate to electroplate any composition of tin and lead as an alloy
Lead(II) iodide	Bronzing, printing, photography, cloud seeding
Lead molybdenum chromate	Analytical chemistry, pigments
Lead(II) nitrate	Lead salts, mordant in dyeing and printing calico, matches, mordant for staining mother of pearl, oxidizer in the dye industry, sensitizer in photography, explosives, tanning, process engraving, and lithography
Lead(II) oxide	Storage batteries, ceramic cements and fluxes, pottery and glazes, glass, chromium pigments, oil refining, varnishes, paints, enamels, assay of precious metal ores, manufacture of red lead, cement (with glycerol), acid-resisting compositions, match-head compositions, other lead compounds, rubber accelerator
Lead(II) phosphate	Stabilizing agent in plastics
Lead(II) styphnate	Primary explosive, firing of Pb-based ammunition
Lead(II) sulfate	Storage batteries, paints, ceramics, pigments, electrical and other vinyl compounds requiring high heat stability
Lead(II) sulfide	Ceramics, infrared radiation detector, semi-conductor, ceramic glaze, source of lead
Tetraethyl lead	Anti-knock agent in aviation gasoline

Sources: Boileau et al. 1987; Carr 1995; Carr et al. 2004; Davidson et al. 2014

Pb arsenate, basic Pb arsenate, and Pb arsenite were formerly used as herbicides, insecticides, or rodenticides. Until the 1960s, they were widely used to control pests in fruit orchards, especially apple

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orchards (EPA 2002c; PAN Pesticides Database 2004; Peryea 1998; Wisconsin DHS 2002). All insecticidal use of Pb arsenate was officially banned on August 1, 1988. However, all registrations for its insecticidal use had lapsed before that time.

5.2.4 Disposal

Secondary (recycled) Pb, derived mainly from scrapped Pb-acid batteries, accounted for 100% of refined Pb production in the United States in 2014. Almost all of the Pb recycled in 2014 was recovered by 7 companies operating 12 plants in Alabama, California, Florida, Indiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas (USGS 2016). More than 99% of all battery Pb is recycled and new batteries contain between 60 and 80% recycled Pb and plastic, respectively (BCI 2019). Scrap Pb is also recovered from dross, dust, residue, and sludge generated by smelting of metals, Pb pipe and sheet, printing materials, sheaths from power and telephone cable, and vehicle wheel weights (USGS 2014).

Disposal of wastes containing Pb or Pb compounds is controlled by several federal regulations (see Chapter 7). Pb is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1988). Pb-containing waste products include storage batteries, ammunition waste, ordnance, sheet Pb, solder, pipes, traps, and other metal products; solid waste and tailings from Pb mining; items covered with Pb-based paint; and solid wastes created by mineral ore processing, iron and steel production, copper and zinc smelting, and the production and use of various Pb-containing products (EPA 1982a).

In the United States., federal laws require, used nickel cadmium (Ni-Cd) and lead (Pb) batteries to be managed as Universal Waste and recycled or disposed of in accordance under Title 40 Parts 266 and 273 of the Code of Federal Regulations (EPA 2020b). The Mercury-Containing and Rechargeable Battery Management Act (the Battery Act) of 1996 removed certain barriers to the recycling of batteries including small, sealed lead acid (SSLA) batteries (EPA 2002b). The intent was to provide the efficient and cost-effective collection and recycling or proper disposal of batteries to keep them out of the waste stream. The Act established uniform national labeling requirements, mandated that batteries under the Act be “easily removable” from consumer products where possible, made the Universal Waste Rule effective in all 50 states for the collection, storage, and transportation of batteries covered by the Battery Act, and

required EPA to establish a public education program on battery recycling and the proper handling and disposal of used batteries (EPA 1997a).

According to data from the TRI, total disposal of Pb and Pb compounds varied during the period of 2005–2015 from 387 million pounds in 2009 to 832 million pounds in 2013, with an overall increase of 20% during this time period. The metal mining sector contributes most to the disposal of Pb and Pb compounds, with metal mines reporting 85% of total Pb and Pb compound releases in 2015.

5.3 RELEASES TO THE ENVIRONMENT

Facilities with ≥ 10 full-time employees in certain industry sectors (e.g., manufacturing) covered by the TRI (e.g., manufacturing) must submit data to TRI on releases and other waste management for TRI-listed chemicals (Pb and Pb compounds are TRI listed). Therefore, TRI data do not reflect all sources of Pb releases (EPA 2005a). TRI-covered facilities are required to report information to the TRI only if they employ the equivalent of ≥ 10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $>25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005a).

Starting in 2001, the threshold to trigger reporting of Pb in most Pb compounds was reduced to 100 pounds. The higher threshold still applies to Pb contained in stainless steel, brass, or bronze alloys. The threshold for Pb is determined using the weight of the metal, whereas the threshold for Pb compounds is determined by the weight of the entire compound. Prior to 1998, only facilities classified within the SIC codes 20–39 (Manufacturing Industries) were required to report. After 1998, the industries required to report were enlarged to include other industrial sectors, such as metal mining, coal mining, electrical utilities, and hazardous waste treatment (EPA 2001).

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Pb is a naturally-occurring element that is typically found combined in various minerals. It occurs in the Earth's crust primarily as the mineral galena (PbS), and to a lesser extent as anglesite (PbSO₄) and cerussite (PbCO₃) (Carr et al. 2004; Davidson et al. 2014; Haynes 2014). Pb minerals are found in association with zinc, copper, and iron sulfides as well as gold, silver, bismuth, and antimony minerals. It also occurs as a trace element in coal, oil, and wood. Typical Pb concentrations in some ores and fuels are: copper ores, 11,000 ppm; Pb and zinc ores, 24,000 ppm; gold ores, 6.60 ppm; bituminous coal, 3–111 ppm; crude oil, 0.31 ppm; No. 6 fuel oil, 1 ppm; and wood, 20 ppm (EPA 2001).

Leaded gasoline remains commercially available for off-road uses, including aircraft, racing cars, farm equipment, and marine engines. Currently, the largest contributor to atmospheric Pb emissions in the United States is piston-engine aircraft emissions (EPA 2016c). Industrial sources of Pb can result from the mining and smelting of Pb ores, as well as other ores in which Pb is a byproduct or contaminant. Fuel combustion also contributes to releases of Pb to the environment. As a result of these processes, Pb may be released to land, water, and air. Many of the anthropogenic sources of Pb have been eliminated or phased out because of Pb's persistence, bioaccumulative nature, and toxicity. These include Pb-based paint in 1978, Pb-containing pesticides in 1988, and Pb in gasoline for use in on-road vehicles in 1996. In early 2017, the use of Pb ammunition and Pb sinkers was banned on most federal lands; however, this ban was temporarily halted soon after. Because Pb does not degrade and remains in the environment long after its release, these former uses continue to be a potential source for Pb exposure.

5.3.1 Air

According to the TRI, in 2018, a total of 57,240 pounds of Pb were released to air from 4,064 reporting facilities (TRI18 2020). In addition, a total of 343,142 pounds of Pb compounds were released to air from 3,789 reporting facilities (TRI18 2020). Tables 5-6 and 5-7 list amounts of Pb and Pb compounds released from these facilities grouped by state, respectively.

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Table 5-6. Releases to the Environment from Facilities that Produce, Process, or Use Lead^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
AK	4	1	0	0	22,766	0	22,167	600	22,767
AL	105	2,944	1,133	11	1,481,278	7,384	1,483,641	9,109	1,492,750
AR	66	2,318	107	0	176,475	730	177,674	1,955	179,629
AZ	52	103	129	0	42,201	331	40,794	1,970	42,765
CA	179	662	1,313	0	585,305	58,212	572,870	72,623	645,493
CO	34	296	20	0	108,291	51	108,414	244	108,658
CT	42	52	541	0	2	5,360	62	5,893	5,955
DC	6	1	2	0	6,493	1,000	6,464	1,031	7,495
DE	6	9	3	89	7,852	0	7,864	89	7,954
FL	221	693	89	1	98,375	15,249	84,880	29,527	114,408
GA	107	3,397	1,000	0	18,503	8,671	20,456	11,114	31,571
GU	1	28	0	0	0	0	0	0	28
HI	2	0	0	0	10,359	0	10,358	1	10,359
IA	114	10,241	80	849	6,205	12,559	14,396	15,538	29,934
ID	27	268	45	0	367,560	29,707	367,635	29,945	397,579
IL	228	3,147	2,286	27	649,364	43,310	613,450	84,683	698,133
IN	160	1,056	272	22	454,088	557,867	7,434	1,005,871	1,013,305
KS	70	536	26	0	24,749	729	13,856	12,183	26,039
KY	79	891	509	0	32,991	5,941	30,618	9,715	40,333
LA	45	511	967	13	22,715	462	22,763	1,905	24,669
MA	55	70	10,245	28	36,566	3,555	15,467	34,998	50,465
MD	34	25	59	0	13,986	86	13,467	689	14,156
ME	20	3	23	0	219	123	39	329	368
MI	147	2,095	396	11	41,090	5,359	19,114	29,837	48,951
MN	123	1,199	232	5	4,017	624	1,971	4,106	6,077
MO	92	483	225	1	20,478	729	12,844	9,072	21,915
MS	62	1,102	35	1	63,143	1,327	63,240	2,368	65,608
MT	13	16	2	0	36,873	0	36,872	20	36,892
NC	162	567	708	248	122,679	1,295	16,540	108,957	125,497
ND	13	1	229	0	6,038	7	6,130	144	6,275
NE	61	4,505	1,379	0	79,160	9,063	83,397	10,709	94,107
NH	29	17	6	0	726	26,933	743	26,939	27,682
NJ	42	198	27	17	3,286	4,976	1,419	7,086	8,505
NM	16	12	0	0	6,472	61	5,582	963	6,545
NV	27	502	1	1	2,554,095	150	2,554,538	210	2,554,748

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-6. Releases to the Environment from Facilities that Produce, Process, or Use Lead^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
NY	140	499	89	0	21,001	9,770	14,560	16,799	31,359
OH	236	4,321	540	232	68,683	33,151	34,929	71,997	106,926
OK	54	451	11	14	81,644	3,422	81,961	3,581	85,542
OR	48	77	45	0	1,495,571	742	1,494,474	1,961	1,496,435
PA	183	6,456	1,908	425	167,238	486,904	12,164	650,767	662,931
PR	4	4	0	0	3,777	47	3,780	48	3,828
RI	14	10	1	0	3	5,086	10	5,091	5,101
SC	80	517	212	0	43,446	947	35,803	9,319	45,123
SD	14	100	0	0	0	25	100	25	126
TN	109	756	222	1	33,156	8,866	21,918	21,083	43,001
TX	325	1,223	1,027	2,833	468,642	45,651	468,737	50,638	519,376
UT	49	835	24	0	95,346	80	89,493	6,793	96,286
VA	93	1,176	574	17	184,110	26,197	83,245	128,828	212,074
VI	3	2	0	0	31	0	24	8	32
VT	11	1	6	0	16,304	397	16,289	419	16,708
WA	54	115	184	0	382,285	212,687	371,196	224,075	595,272
WI	163	1,921	638	0	35,520	13,924	5,242	46,762	52,004
WV	30	410	190	52	144,313	38	144,201	803	145,004
WY	10	416	1	0	47,579	1	47,733	263	47,996
Total	4,064	57,240	27,764	4,901	10,393,047	1,649,785	9,363,048	2,769,688	12,132,737

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred offsite, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI18 2020 (Data are from 2018)

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Table 5-7. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
AK	15	19,345	139	0	499,679,935	1,006	499,696,960	3,465	499,700,425
AL	130	6,801	4,859	0	1,254,651	4,503	1,167,133	103,682	1,270,814
AR	67	5,268	1,098	0	481,839	53,191	239,131	302,264	541,396
AZ	64	64,290	103	0	27,547,626	7,110	27,600,302	18,827	27,619,128
CA	305	5,816	435	0	2,656,973	27,145	1,127,596	1,562,773	2,690,369
CO	76	2,931	244	1	10,195,005	239	10,180,490	17,930	10,198,420
CT	39	445	565	0	32,116	14,510	708	46,929	47,637
DC	1	0	0	0	24	0	24	0	24
DE	5	127	17	0	489	1,070	599	1,103	1,703
FL	150	5,429	1,691	1	972,024	2,470	946,498	35,116	981,615
GA	107	6,011	4,228	0	573,267	242	361,887	221,860	583,747
GU	3	30	0	0	1,510	0	1,540	0	1,540
HI	14	2,406	35	18	57,605	4	57,568	2,501	60,068
IA	66	3,101	568	4	98,007	47,899	35,369	114,209	149,578
ID	31	1,337	105	0	587,617	1,071	588,601	1,529	590,130
IL	163	10,458	3,316	158	1,044,749	382,696	219,957	1,221,420	1,441,377
IN	147	26,832	60,668	86	3,554,799	1,702,496	1,345,912	3,998,968	5,344,880
KS	40	2,171	126	35	33,471	7,290	31,594	11,499	43,092
KY	64	15,233	719	272	758,794	116,393	739,954	151,456	891,411
LA	82	8,193	8,065	303	694,825	3,582	504,890	210,078	714,968
MA	53	888	357	0	20,874	2,919	2,655	22,382	25,037
MD	35	209	203	0	4,611	55,261	1,443	58,842	60,285
ME	13	750	510	0	23,485	8,099	4,729	28,116	32,844
MI	100	4,220	979	13	2,091,026	18,914	1,514,558	600,594	2,115,152
MN	50	2,961	291	0	980,965	2,228	97,635	888,810	986,445
MO	73	12,990	1,919	206	18,739,390	243,396	18,118,610	879,290	18,997,900
MP	1	2	0	0	1	0	3	0	3
MS	50	2,260	1,770	197,869	261,610	3,066	235,034	231,540	466,575
MT	20	3,438	20	4,503	6,091,825	581	6,092,803	7,565	6,100,367
NC	145	10,843	973	0	728,520	35,993	551,282	225,047	776,329
ND	19	4,103	19	0	90,847	5,984	76,746	24,207	100,953
NE	24	1,473	125	0	50,473	529	46,977	5,623	52,600
NH	14	20	23	0	1,509	6,243	94	7,702	7,796
NJ	54	871	12,266	0	410,073	234,474	62,349	595,336	657,685
NM	17	902	283	1	2,978,296	31,276	2,893,375	117,383	3,010,758
NV	49	9,161	1	0	49,276,056	40	49,282,572	2,685	49,285,258
NY	82	2,294	1,167	0	209,644	26,579	132,597	107,087	239,684

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Table 5-7. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds^a

		Reported amounts released in pounds per year ^b							
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
OH	175	9,346	17,583	5,952	1,483,307	263,386	1,093,350	686,224	1,779,574
OK	80	11,075	378	58	307,485	945	307,785	12,157	319,941
OR	55	1,591	2,127	0	5,176	1,827	6,272	4,449	10,721
PA	195	13,623	15,874	0	3,488,454	229,953	3,176,873	571,031	3,747,904
PR	11	759	13	0	236	1,300	772	1,536	2,308
RI	19	23	15	0	1,018	124	24	1,155	1,179
SC	100	4,198	1,783	0	459,973	38,536	101,830	402,660	504,490
SD	11	149	0	0	1,757,845	9	1,757,955	48	1,758,003
TN	89	4,151	2,653	184	3,375,608	11,693	2,953,656	440,633	3,394,289
TX	323	14,625	2,732	2,309	1,365,901	3,582	1,170,161	218,988	1,389,149
UT	40	17,378	657	0	185,430,965	41,774	185,290,906	199,868	185,490,774
VA	82	10,922	8,300	0	201,670	12,410	206,084	27,217	233,301
VI	2	13	0	0	0	0	13	0	13
VT	5	10	0	0	117	0	10	117	127
WA	76	4,205	843	0	2,976,519	10,118	2,925,078	66,607	2,991,685
WI	98	3,448	1,598	0	279,692	27,606	74,486	237,858	312,344
WV	44	3,235	920	0	362,089	1,142	240,520	126,866	367,385
WY	16	783	2	0	79,050	284	67,659	12,461	80,119
Total	3,789	343,142	163,361	211,975	833,759,635	3,693,189	823,333,608	14,837,694	838,171,302

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II–V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other offsite management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred offsite, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI18 2020 (Data are from 2018)

The decrease in national Pb emissions between 1970 to 2011 is estimated to be 99.6% (220,000 tons), which is mostly attributed to the elimination of leaded gasoline for on-road vehicles. Since 2000, nonroad engines and metals industrial processing have accounted for most of the anthropogenic Pb emissions in the United States (EPA 2015). Based on data from the National Emissions Inventory (NEI 2014), the following sectors contribute the largest portions of total Pb emissions in the United States: mobile-aircraft (63%), industrial processes—not elsewhere classified (6.8%), industrial processes—ferrous metals (6.8%), fuel combustion—electric generation—coal (5.5%), and industrial processes—non-ferrous metals (4.1%) (EPA 2016c). Historical trends of Pb emissions in the United States are provided in Table 5-8 (EPA 2015).

Table 5-8. Historic Levels of Lead Emissions to the Atmosphere in the United States (in Thousand Metric Tons)

	1970	1975	1980	1985	1990	1995	1999	2002	2005	2008	2011
On-road vehicles	172	130.2	60.5	18.1	2.17	2.05	1	0	0	0	0
Metals industrial processing	24.22	9.923	3.03	2.1	0.5	0.49	0.96	0.4	0.3	0.16	0.14
Fuel combustion	10.62	10.35	4.3	0.52	0.42	0.02	0	0.39	0.14	0.12	0.09
Nonroad engines	9.737	6.13	4.2	0.92	0.78	0.54	0.55	0.45	0.66	0.56	0.49
Other sources	4.331	3.053	2.12	1.31	1.11	0.83	0.84	0.43	0.25	0.11	0.1

Source: EPA 2015

According to the data from the NEI, the largest portions of total Pb emissions are in the U.S. mobile-aircraft sector. Murphy et al. (2008) studied weekly patterns of metals and other aerosol components using data collected from 2000 to 2006 at Interagency Monitoring of Protected Visual Environments (IMPROVE) sites, and these data suggested that Pb concentrations were impacted by piston aircraft emissions.

As indicated in Table 5-6, by the early 2000s, transportation (i.e., automotive) emissions were no longer the dominant source of Pb emitted to the atmosphere. When such emissions were prevalent, >90% (mass basis) of automotive Pb emissions from leaded gasoline were in the form of inorganic particulate matter (e.g., Pb bromochloride [PbBrCl]) and <10% (mass basis) were in the form of organolead vapors (e.g., Pb alkyls). In 1984, the average Pb content of gasoline was 0.44 g Pb/gallon (EPA 1986b); however, as of January 1986, the allowable Pb content of leaded gasoline dropped to 0.1 g Pb/gallon (EPA 1985d). Between January and June of 1990, the actual average Pb concentration in leaded gasoline was 0.085 g Pb/gallon, indicating consumption of approximately 230,000 kg of Pb for the production of 2.74 billion

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gallons of leaded gasoline. In the early 1980s, EPA allowed up to 0.05 g of Pb in a gallon of unleaded gasoline (EPA 1982b).

According to data from TRI, on-site air releases of Pb and Pb compounds varied over the same period from 431,311 pounds in 2014 to 1,037,265 pounds in 2006, with an overall decrease of 40%. In 2018, 91,028 pounds of Pb and Pb compounds were released to air. The electric utility and primary metals industry sectors contributed to this overall decrease; both sectors have decreased air Pb and Pb compounds releases by approximately 70% from 2005 to 2015. The primary metal sector, which includes iron and steel manufacturers and smelting operations, contributes the greatest quantity of Pb and Pb compounds to air releases (EPA 2017a, 2017b).

While Pb levels in paints for interior use have been restricted since the 1950s, older houses and furniture may still be covered with leaded paint. Releases from Pb-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint by sanding or sandblasting can result in high localized concentrations of Pb dust in both indoor and outdoor air.

The largest volume of organolead vapors released to the atmosphere results from industrial processes; prior to its phaseout and ban, leaded gasoline containing tetraethyl Pb as an anti-knock additive was also a major contributor. Tetraalkyl Pb vapors are photoreactive, and their presence in local atmospheres is transitory. Halogenated Pb compounds are formed during combustion by reaction of the tetraalkyl Pb compounds with halogenated Pb scavenger compounds. These halogenated Pb compounds ultimately give rise to Pb oxides and carbonates in the environment (EPA 1985b). Tetraalkyl Pb compounds once contributed 5–10% of the total particulate Pb present in the atmosphere. Organolead vapors were most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, and parking garages) and high-traffic areas (Nielsen 1984).

5.3.2 Water

According to the TRI, in 2018, a total of 27,764 pounds of Pb were released to water from 4,064 reporting facilities (TRI18 2020). In addition, a total of 163,361 pounds of Pb compounds were released to water from 3,789 reporting facilities (TRI18 2020). Tables 5-6 and 5-7 list amounts of Pb and Pb compounds released from these facilities grouped by state, respectively.

The following industry sectors accounted for the majority of release of Pb to surface water in 2018: chemicals (14%); paper (12%); primary metals (10%); transportation equipment (5%); and fabricated metals (2%). The following industry sectors accounted for the majority of release of Pb compounds to surface water in 2018: paper (20%); electric utilities (8%); primary metals (8%); metal mining (3%) (TRI18 2020). The trends in discharges of Pb and Pb compounds to surface water from 2001 to 2018 are presented in Table 5-9.

Table 5-9. U.S. Surface Water Discharges of Lead and Lead Compounds (Pounds/Year)

Year	Lead	Lead compounds
2001	45,871	97,479
2002	20,694	92,366
2003	21,314	109,299
2004	14,564	107,386
2005	15,883	100,778
2006	22,985	86,772
2007	16,745	82,815
2008	11,404	153,681
2009	9,886	73,683
2010	7,263	72,556
2011	7,086	77,568
2012	7,307	60,656
2013	6,327	76,053
2014	8,836	79,344
2015	5,264	70,981
2016	9,507	119,566
2017	11,901	100,552
2018	9,943	105,473

Source: EPA 2017c; TRI18 2020

Data reported by Environment and Climate Change Canada (2016) show that other industries, which include the iron and steel industry, oil and gas industry, and cement and concrete industry, contributed 136.9 tonnes of the total Pb released to water in 2014. This release includes 134.1 tonnes of Pb that were released when a dam securing a tailings pond from the Mount Polley mine in central British Columbia breached on August 4, 2014, spilling mining waste into Polley Lake and surrounding waters. Waste, pulp, paper, and paperboard industry, and non-ferrous smelting and refining were the next largest contributors (Table 5-10). In 2013, Pb releases to water were similar for other industries and waste.

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Table 5-10. Canada Surface Water Discharges of Lead and Lead Compounds (Tonnes)

Year	Other industries	Waste	Pulp, paper, and paperboard industry	Non-ferrous smelting and refining	Other sources
2003	4.38	15.49	2.55	1.74	0.18
2004	3.97	11.53	2.84	2.26	0.26
2005	6.11	9.47	3.29	1.82	0.58
2006	5	9.9	2.35	1.65	0.24
2007	3.63	6.42	2.37	1.64	0.19
2008	4.76	11.58	2.42	2.04	0.16
2009	3.39	8.49	2.25	2.13	0.19
2010	3.21	11.97	2.12	1.45	0.14
2011	3.65	8.97	2.91	1.5	0.16
2012	4.66	4.69	2.8	1.75	0.12
2013	4.17	4.66	2.42	1.48	0.13
2014	136.92	5.11	1.85	1.77	0.13

Source: Environment and Climate Change Canada (2016)

Urban runoff and atmospheric deposition are significant indirect sources of Pb found in the aquatic environment. Pb reaching surface waters is sorbed to suspended solids and sediments (EPA 1982a; EPA 2006, 2014c).

Pb is released into surface water from Pb shot and Pb sinkers. A study of a shooting range in Southwestern Virginia found that the dissolved Pb content of surface water ranged up to 473 ppb, with the highest concentrations closest to the backstop (Craig et al. 1999). Upstream from the site, the Pb concentration was 0.5 ppb. In 1991, the U.S. Fish and Wildlife Service banned the use of Pb shot when hunting waterfowl, such as geese or ducks, in order to avoid releasing Pb directly to surface water.

5.3.3 Soil

According to the TRI, in 2018, a total of 10,393,047 pounds of Pb were released to the land, both on-site and off-site, by 4,064 reporting facilities (TRI18 2020). Table 5-6 lists amounts of Pb released from these facilities grouped by state. In addition, a total of 833,759,635 pounds of Pb compounds were released to land, both on-site and off-site, by 3,789 reporting facilities (TRI18 2020). Table 5-7 lists amounts of Pb compounds released from these facilities grouped by state. In addition, 27,764 and 211,975 pounds of Pb and Pb compounds, respectively, were injected underground.

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Pb-containing material from home and commercial use may be sent to municipal landfills. It is important to note that land is the ultimate repository for Pb, and Pb released to air and water ultimately is deposited in soil or sediment. For example, Pb released to the air from leaded gasoline or in stack gas from smelters and power plants will settle on soil, sediment, foliage, or other surfaces. The heaviest contamination occurs near the highway, in the case of leaded gasoline, or near the facility, in the case of a power plant or smelter. Road dust contributes to Pb in soil. Pb concentrations were higher in surface soils within 1,000 m of roadways (134 kg/ha) as compared to outside the 1,000-m region (38.7 kg/ha) (Yesilonis et al. 2008). Wheel weights can contribute to releases of Pb along roadways. Aucott and Caldarelli (2012) estimated that approximately 12 tons of Pb as wheel weights are deposited on New Jersey roadways; however, they estimated that only a small amount enters the environment as small particulate from grinding. Root (2000) also estimated a rate of Pb deposition in Albuquerque, New Mexico as 50–70 kg/km/year. However, use of Pb wheel weights are on the decline due to legislation, voluntary phase-out, and new wheel technology (Aucott and Caldarelli 2012).

5.3.4 Paint

Although the sale of residential Pb-based paint was banned in the United States in 1978, flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, remain major sources of Pb exposure for young children residing in these houses, particularly for children afflicted with pica (the compulsive, habitual consumption of nonfood items) (Bornschein et al. 1986; EPA 1986b). Pb concentrations of 1–5 mg/cm² have been found in chips of Pb-based paint (Billick and Gray 1978), suggesting that consumption of a single chip of paint would provide greater short-term exposure than any other source of Pb (EPA 1986b). An estimated 40–50% of occupied housing in the United States may contain Pb-based paint on exposed surfaces (Chisolm 1986).

In the late 1980s, the U.S. Department of Housing and Urban Development (HUD) conducted a national survey of Pb-based paint in housing. The EPA subsequently sponsored a comprehensive technical report on the HUD-sponsored survey to provide estimates of the extent of Pb-based paint in housing. In the EPA report, a home is considered to have Pb-based paint if the measured Pb concentration on any painted surface is ≥ 1.0 mg/cm². The EPA report estimates that 64 million (± 7 million) homes, or 83% ($\pm 9\%$) of privately-owned housing units built before 1980, have Pb-based paint somewhere in the building. Approximately 12 million (± 5 million) of these homes are occupied by families with children under the age of 7 years. Approximately 49 million (± 7 million) privately owned homes have Pb-based paint in

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their interiors. By contrast, approximately 86% ($\pm 8\%$) of all pre-1980 public housing family units have Pb-based paint somewhere in the building (EPA 1995b).

Damaged Pb-based paint is associated with excessive dust Pb levels. Approximately 14 million homes (19% of pre-1980 housing) have >5 square feet of damaged Pb-based paint, and nearly half (47%) of those homes have excessive dust Pb levels (EPA 1995b).

In the Cincinnati prospective Pb study of public and private low- and moderate-income housing, the Pb concentration ranges were: painted interior walls, 0.1–35 mg/cm²; interior home surface dust, 0.04–39 mg/m² and 72–16,200 $\mu\text{g/g}$; interior home dustfall, 0.0040–60 mg/m²/30 days; exterior dust scrapings, 20–108,000 $\mu\text{g/g}$; and dust on children's hands, 1–191 μg . The Pb levels in older private deteriorating or dilapidated housing were higher than the levels in newer public and rehabilitated housing (Clark et al. 1985).

Releases from Pb-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of Pb in dust in air (from sanding and sandblasting) and on exposed surfaces. A study was conducted in New Orleans where power sanding is a common practice during repainting old houses; median, 90th percentile, and maximum Pb concentrations in 31 study houses were 35, 126, and 257 mg/g, respectively (Mielke et al. 2001). Pb concentrations in dust and soil samples from one study of a house where the paint chips contained about 90 mg Pb/g were very high. If the house had been sanded down to bare wood, 7.4 kg of Pb would have been released to the environment. Disturbance of older structures containing Pb-based paints is now a significant contributor to total Pb releases.

The authors of a report of findings from NHANES III, conducted in 1988–1991, commented that of the multiple sources of exposure, Pb-based paint is the principal high-dose source of Pb. Exposure occurs not only through the direct ingestion of flaking and chalking paint, but also through the inhalation of dust and soil contaminated with paint (Brody et al. 1994). According to a study by the New York State Department of Health, renovation and remodeling activities that disturb Pb-based paints in homes can produce significant amounts of Pb dust, which can be inhaled or ingested (CDC 1997a).

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5.4 ENVIRONMENTAL FATE

The atmosphere is the main environmental transport media for Pb that is deposited onto surface water and soils (EPA 2006, 2014c). Upon release to the atmosphere, Pb particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Pb deposition is typically greatest closer to Pb emission sources. An important factor in determining the atmospheric transport of Pb is particle size distribution. Large particles settle out of the atmosphere more rapidly and are deposited relatively close to emission sources and smaller particles may be transported much farther distances. After deposition, particles may be resuspended and redeposited. The cycling of Pb in aquatic environments is governed by chemical, biological, and mechanical processes. The exchange between sediment and surface water will be affected by pH, ionic strength, formation of organic complexes with Pb ions, and oxidation-reduction potential of the environment (EPA 2006, 2014c).

5.4.1 Transport and Partitioning

Transport and partitioning of Pb in the environment is an interplay of various processes (EPA 2014c). Global atmospheric deposition of Pb peaked in the 1970s and has declined since then; however, these deposits are still in the environment and can be transported and partitioned between environmental compartments. Past and current releases of Pb to the air result in the deposition of Pb on land and in surface water. While soil is a repository for Pb, it is not a passive repository, and resuspension of Pb contaminated soil-derived dust particulates can contribute to Pb exposure (Laidlaw and Filippelli 2008; Laidlaw et al. 2012). Pb in soil can be washed off surfaces into waters, and within water, it can partition between water and sediments (EPA 2006, 2014c).

Air. EPA (2006) summarized that the major pathway for the transport of Pb in the environment is the atmosphere and that airborne Pb tends to be in the form of submicron aerosols, which can travel large distances. After release to the atmosphere, Pb particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Dry deposition was the major removal process for Pb in coarse particulate matter and wet deposition was the most important removal process for fine particulate matter. Soil-bound Pb and contaminated road dust can be resuspended and can be a significant source of airborne Pb in areas near major sources of Pb emissions (EPA 2006, 2014c).

In the atmosphere, non-organic compounds of Pb exist primarily in the particulate form. The median particle distribution for Pb emissions from smelters is 1.5 μm , with 86% of the particle sizes under 10 μm

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(Corrin and Natusch 1977). The smallest Pb-containing particulate matter ($<1\ \mu\text{m}$) is associated with high-temperature combustion processes. Upon release to the atmosphere, Pb particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Approximately 40–70% of the deposition of Pb is by wet fallout; 20–60% of particulate Pb once emitted from automobiles is deposited near the source. An important factor in determining the atmospheric transport of Pb is particle size distribution. Large particles, particularly those with aerodynamic diameters of $>2\ \mu\text{m}$, settle out of the atmosphere more rapidly and are deposited relatively close to emission sources (e.g., 25 m from the roadway for those size particles emitted in motor vehicle exhaust in the past); smaller particles may be transported thousands of kilometers away from the emission source.

The amount of Pb scavenged from the atmosphere by wet deposition varies widely; wet deposition can account for 40–70% of Pb deposition depending on such factors as geographic location and amount of emissions in the area (Nielsen 1984). An annual scavenging ratio (concentration in precipitation, mg/L, to concentration in air, $\mu\text{g}/\text{m}^3$) of 0.18×10^{-6} has been calculated for Pb, making it the lowest value among seven trace metals studied (iron, aluminum, manganese, copper, zinc, cadmium); this indicates that Pb (which initially exists as fine particles in the atmosphere) is removed from the atmosphere by wet deposition relatively inefficiently.

While Pb particles from automobile emissions are quite relatively small ($<0.1\ \mu\text{m}$ in diameter), they may coagulate to form larger particulates (Chamberlain et al. 1979). Pb has been found in sediment cores of lakes in Ontario and Quebec, Canada far from any point sources of Pb releases, suggesting that long-range atmospheric transport was occurring (Evans and Rigler 1985). Sabin and Schiff (2008) reported that median dry deposition fluxes along a coastal transect in southern California ranged from 0.52 to $14\ \mu\text{g}/\text{m}^2\text{-day}$ in 2006. Pb fluxes ranged from 20 to $330\ \mu\text{g}/\text{m}^2\text{-day}$ in 1975. Osterberg et al. (2008) reported elevated concentrations of Pb in a 1970–1998 ice core from the summit of Mt. Logan, Canada, and indicated that elevated levels correspond to increased industrial activity in Asia over the same time period. Mean Pb concentrations in the 1970–1998 portion were 68.9 ng/L, more than 10-fold above the natural background (5.6 ng/L).

Pb in soil in urban areas of older cities may be a source of airborne Pb (Laidlaw and Filippelli 2008). Studies of the Pb species found in airborne particulate matter collected in El Paso, Texas found that Pb-humate was the dominant form of Pb in air samples. Pb-humate, a stable, sorbed complex formed in the humus fraction of Pb contaminated soil, is the major Pb species in soils in El Paso (Pingitore et al. 2009). In a review, Cho et al. (2011) noted that, over the past 40 years, lead-bound air particulates have shifted to

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larger air particulate sizes as concentrations of Pb in urban areas have decreased. They note that this shift has occurred as the use of leaded gasoline was phased-out and that industrial emissions and resuspension of road dust became more important sources of Pb. In addition to soil-derived dust, re-entrainment of dusts near highways and deteriorating Pb-based paint from elevated steel structures can contribute to airborne Pb (Sabin et al. 2006; Weiss et al. 2006). Studies suggest that there is long-range transport of Pb bound to particulate matter from industrial emissions. Dust samples from surface glaciers and in dust traps in remote areas on the west coast of New Zealand's South Island were identified as being both Australian and New Zealand in origin. Samples were enriched in metals, including Pb, and the degree of metal enrichment indicated that they were transported from eastern Australia (Marx et al. 2008).

Water. The amount of soluble Pb in surface waters depends upon the pH and the ionic strength of the water. Equilibrium calculations show that at $\text{pH} > 5.4$, the total solubility of Pb is approximately 30 $\mu\text{g/L}$ in hard water and approximately 500 $\mu\text{g/L}$ in soft water. Sulfate ions, if present in soft water, limit the Pb concentration in solution through the formation of Pb sulfate. Above pH 5.4, the Pb carbonates, PbCO_3 and $\text{Pb}_2(\text{OH})_2\text{CO}_3$, limit the amount of soluble Pb. The carbonate concentration is in turn dependent upon the partial pressure of carbon dioxide, pH, and temperature (EPA 1986b).

A significant fraction of Pb carried by river water is expected to be in an undissolved form, which can consist of colloidal particles or larger undissolved particles of Pb carbonate, Pb oxide, Pb hydroxide, or other Pb compounds incorporated in other components of surface particulate matter from runoff. Pb may occur either as sorbed ions or surface coatings on sediment mineral particles, or it may be carried as a part of suspended living or nonliving organic matter in water.

Sediment and Soil. EPA (2006, 2014c) reviewed and summarized the factors affecting the behavior of Pb in soil. While Pb is relatively immobile in soil and has a long retention time in most soils, it has some capacity to leach through the soil column and potentially contaminate groundwater. Pb sorbs strongly to soil components and is only weakly soluble in pore water, making the leaching of Pb in soil a slower process as compared to other contaminants. Various soil conditions and characteristics affect the sorbing capacity of the soil and the solubility of contaminants including hydraulic conductivity of the soils, composition of the soil solution, organic matter, clay mineral content of the soil, pH, and microbial activity (EPA 2006). In soil, Pb can be partitioned between the soil water, precipitate forms, secondary iron and manganese oxides, carbonates, organic matter, sulfides, or the surfaces of clay, humus, or silicate particles. Pb adsorbed to the surfaces of colloid soil particles (e.g., organic matter, clay, oxides, and carbonates) are the most labile fraction. High chloride content in soil also enhances Pb solubility. At low

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pH, metal species bound to carbonates, hydroxides, and other soil components are more likely to dissolve into solution, increasing rates of Pb migration through the soil. EPA (2014c) reported that soil pH is the most important factor affecting solubility, mobility, and phytoavailability of Pb in soil; however, reducing conditions (e.g., anoxia) in soil also increase Pb mobility. In addition, dissolved organic matter is more important than iron oxyhydroxides in Pb mobility in soil.

The fate of Pb in soil is affected by the adsorption at mineral interfaces, precipitation of sparingly soluble solid forms of the compound, and formation of relatively stable organic-metal complexes or chelates with soil organic matter. These processes are dependent on such factors as soil pH, soil type, particle size, organic matter content of soil, presence of inorganic colloids and iron oxides, cation exchange capacity (CEC), and amount of Pb in soil (Getz et al. 1977; Reddy et al. 1995). Soil samples were extracted from the Powder River Basin in Wyoming to determine the relative distribution and speciation of Pb and other metals in acidic environments (Reddy et al. 1995). At near neutral pH, organic carbon-Pb complexes were the predominant species in the soil water extracts. At low pH, dissolved Pb in ionic form (Pb^{2+}) and ion pairs (e.g., PbSO_4) were the predominant species. It was concluded that the mobility of Pb will increase in environments having low pH due to the enhanced solubility of Pb under acidic conditions. The accumulation of Pb in most soils is primarily a function of the rate of deposition from the atmosphere. Most Pb is retained strongly in soil, and very little is transported through runoff to surface water or leached to groundwater except under acidic conditions (EPA 1986b; Getz et al. 1977). Clays, silts, iron and manganese oxides, and soil organic matter can bind metals electrostatically (cation exchange) as well as chemically (specific adsorption) (Reed et al. 1995). Although sorption to organic matter in soil limits the rate and extent of leaching, Pb may enter surface waters as a result of erosion of Pb-containing soil particulates. Pb bromochloride, the primary form of Pb emitted from motor vehicles, which once burned leaded gasoline in the presence of organohalogen scavenger compounds, is converted to the less-soluble Pb sulfate either by reactions in the atmosphere or by reactions at the soil surface, thus limiting its mobility in soil. It has been determined that Pb oxides, carbonates, oxycarbonates, sulfates, and oxysulfates become the most prominent constituents of aged automobile exhaust particles (i.e., those collected at locations more remote from traffic sources) (Ter Haar and Bayard 1971). Pb may also be immobilized by ion exchange with hydrous oxides or clays or by chelation with humic or fulvic acids in the soil (Olson and Skogerboe 1975). In soils with $\text{pH} \geq 5$ and with at least 5% organic matter content, atmospheric Pb is retained in the upper 2–5 cm of undisturbed soil. Inorganic Pb may be bound into crystalline matrices of rocks and remain essentially immobile; it can also occur in water entrapped in soil macro- and micropores (Reed et al. 1995). In soil with high organic matter content and a pH of 6–8, Pb may form insoluble organic Pb complexes; if the soil has less organic matter at the same pH, hydrous Pb

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oxide complexes may form or Pb may precipitate out with carbonate or phosphate ions. At a pH of 4–6, the organic Pb complexes become soluble and leach out or may be taken up by plants (EPA 1986b). Entrainment or suspension of soil particles in moving air is another route of Pb transport (EPA 1982c). This process may be important in contributing to the atmospheric burden of Pb around some Pb smelting facilities and NPL sites that contain elevated levels of Pb in soil.

The downward movement of elemental Pb and inorganic Pb compounds from soil to groundwater by leaching is very slow under most natural conditions except for highly acidic situations (Getz et al. 1977). The conditions that induce leaching are the presence of Pb in soil at concentrations that either approach or exceed the CEC of the soil, the presence of materials in soil that are capable of forming soluble chelates with Pb, and a decrease in the pH of the leaching solution (e.g., acid rain) (Getz et al. 1977). Favorable conditions for leaching may be present in some soils near Pb smelting and NPL sites. Tetraalkyl Pb compounds, such as tetraethyl Pb, are insoluble in water and would not be expected to leach in soil. However, they can be transported through a soil column when it is present in a migrating plume of gasoline (USAF 1995). In aqueous media, tetraalkyl Pb compounds are first degraded to their respective ionic trialkyl Pb species and are eventually mineralized to inorganic Pb (Pb^{2+}) by biological and chemical degradation processes (Ou et al. 1995).

In a study of Pb migration in forest soils in Vermont, Miller and Friedland (1994) used Pb deposition time series and measurements of organic soil horizon Pb content made in 1966, 1980, and 1990 to compute dynamic response times for Pb storage in several types of soil. The authors concluded that maximum Pb concentrations in organic soil occurred around 1980, with concentrations of about 85 $\mu\text{g/g}$ in soils of the northern hardwood forests of the study area and about 200 $\mu\text{g/g}$ in soils of the spruce-fir forests. The large surge of atmospheric Pb deposited in these forests during the time when leaded gasoline was routinely used in motor vehicles is being redistributed in the soil profile rather than being retained in the organic horizon. Based on an analysis of Pb transit times through mineral soil horizons, the pulse of Pb may begin to be released to upland streams sometime in the middle of the next century (Miller and Friedland 1994). However, Wang et al. (1995) observed that Pb migration in forest soils is slowed considerably due to a decrease in solubility when Pb moves from the soil surface horizon to streams. Their results suggest that Pb is effectively trapped in the subsurface soil horizons, which may greatly reduce its release to streams.

Lewis et al. (2010) studied the distribution, chemical speciation, and mobility of Pb and antimony from small arms ammunition in a coarse-grained surface sand and reported that the transport of Pb was small in

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this soil type. Ninety-three percent of the mass of the bullets was found in the top 30 cm of the sand. Pb was mostly associated with the following grain sizes in decreasing order >5.0 mm (~3.3 g/kg), 1.2–5.0 mm (~1.5 g/kg), and <0.06 mm (~0.25 mg/kg). In the 0.06–0.6 mm fractions, Pb concentrations were just above background levels (0.0004 g/kg). Declining concentrations with depth has also been observed in clay/loam shooting range soils (Vantelon et al. 2005). Pb in the fine fraction (<2 mm) shooting range soils also showed a depth distribution, with the highest concentrations in the top 10 cm (Cao et al. 2003a, 2003b; Hui et al. 2002; Lin et al. 1995; Perroy et al. 2014; Selonen et al. 2012). In a study of various contaminant levels in soil at a major training facility used for testing military tanks and munitions, Pb concentrations in the 0–15 cm soil depth ranged from 249.2 to 1,963.7 mg/kg (Berthelot et al. 2008).

Flooding events can change the spatial distribution of Pb in soil and sediments (EPA 2014c). Zahran et al. (2010) and Presley et al. (2010) reported variations in Pb concentrations in soil samples from schoolyards in New Orleans, Louisiana before and after Hurricanes Katrina and Rita in 2005, with some sites increasing and others decreasing in Pb concentrations. Forty-six census tracts in New Orleans were sampled before and after Hurricanes Katrina and Rita; 29 of these showed a decline in Pb concentrations, with 6 samples >400 mg/kg. Prior to these hurricanes, 15 of 46 samples had Pb concentrations >400 mg/kg. Across the tracts, the average median Pb concentration decreased from 328.5 to 203.33 mg/kg (Zahran et al. 2010). Presley et al. (2010) reported similar trends. Of the 17 schoolyard sites that were sampled, 7 sites had concentrations exceeding Pb concentrations of 400 mg/kg in June 2005, and in January 2006, Pb concentrations at 3 sites exceeded this concentration. The geometric mean concentration of the sites decreased from 290.0 to 207.4 mg/kg; however, at two sites, Pb concentrations increased from 804.0 to 1,740.0 mg/kg and from 1,090.0 to 2,500.0 mg/kg. During a 4-day storm event, 2,400 tonnes of suspended particulate matter were transported in a historical mining, ore processing, and smelting region in the Czech Republic that contained various metals including 2,954 kg of Pb (Žák et al. 2009).

Other Media. Plants and animals may bioconcentrate Pb, but biomagnification is not expected. In general, the highest Pb concentrations are found in aquatic and terrestrial organisms with habitats near Pb mining, smelting, and refining facilities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage sludge and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting and fishing (Pb from spent shot or sinkers); and urban and industrialized areas. Pb may be present on plant surfaces as a result of atmospheric deposition; its presence in internal plant tissues indicates biological uptake from the soil and leaf surfaces. Although the bioavailability of Pb in soil to plants is limited because of the strong adsorption of Pb to soil organic matter, bioavailability

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increases with increased soil organic matter content and with decreased soil pH (more acidic). Plants grown in Pb-contaminated soils were shown to accumulate low levels of Pb in the edible portions of the plant from adherence of dusts and translocation into the tissues (Finster et al. 2004). Thirty-two different types of fruits or vegetables were grown in urban gardens with soils containing high Pb levels (27–4,580 mg/kg). Samples were harvested and washed with either water or detergents and analyzed for Pb content. Only one fruiting vegetable among 52 samples contained Pb levels greater than the detection limit of 10 µg/g in the edible portion. However, 39% of the leafy vegetables and herbs had Pb levels >10 µg/g in the edible shoot portion following washing of the vegetables with detergent and water (Finster et al. 2004).

Pb may be taken up in edible plants from the soil via the root system, by direct foliar uptake and translocation within the plant, and by surface deposition of particulate matter. The amount of Pb in soil that is bioavailable to a vegetable plant depends on factors such as cation exchange capacity, pH, amount of organic matter present, soil moisture content, and type of amendments added to the soil. Background agricultural soil Pb concentrations for major growing areas of the United States have been determined (Holmgren et al. 1993).

The influence of various combinations of soil amendments on Pb uptake by soybeans was studied for a metal-contaminated alluvial soil (Pierzynski and Schwab 1993). Addition of limestone was found to be most effective in reducing the bioavailability of metals (including Pb) as indicated by the reduction in labile soil metals, increased yields, and decreased soybean tissue metal content. Uptake of metals by lettuce and radishes grown in a loam soil spiked with cadmium chloride and Pb nitrate (from 100 to 1,000 mg/kg) was also studied (Nwosu et al. 1995). Results indicated that the mean uptake of Pb by lettuce increased as the concentration of Pb rose in the soil mixture. However, the uptake was low and this finding is inconsistent with other reports. Pb was not bioaccumulated by either plant regardless of soil Pb concentrations. The response of kidney bean growth to the concentration and chemical form of Pb in soils obtained near a zinc smelter in Japan has been studied (Xian 1989). It was found that the amount of Pb in the total plant (approximately 35–80 µg) correlated strongly with the concentration of Pb in the soil (0–240 mg/kg). The best relationship was found between the amount of metal uptake and the concentration of exchangeable and carbonate forms of Pb in the soil.

Uptake of Pb in animals may occur as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. However, Pb is not biomagnified in aquatic or terrestrial food chains. Older organisms tend to contain the greatest body burdens of Pb. In aquatic organisms, Pb concentrations are

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usually highest in benthic organisms and algae, and lowest in upper trophic level predators (e.g., carnivorous fish). Exposure of a fresh water fish to several sublethal concentrations of Pb for a period of 30 days showed significant accumulation of Pb in the blood and tissues. The Pb accumulation in tissues was found to increase with Pb in water up to a concentration of 5 mg/L ($\mu\text{g/mL}$); at concentrations of 10 and 20 mg/L, the Pb accumulation in the tissues, although indicating an increase, was not proportional to the Pb concentration in water (Tulasi et al. 1992). High bioconcentration factors (BCFs) were determined in studies using oysters (6,600 for *Crassostrea virginica*), fresh water algae (92,000 for *Senenastrium capricornutum*), and rainbow trout (726 for *Salmo gairdneri*). However, most median BCF values for aquatic biota were significantly lower: 42 for fish, 536 for oysters, 500 for insects, 725 for algae, and 2,570 for mussels (Eisler 1988). Pb is toxic to all aquatic biota, and organisms higher up in the food chain may experience Pb poisoning as a result of eating Pb-contaminated food. Organolead compounds, such as trialkyl and tetraalkyl Pb compounds, are more toxic than inorganic forms and have been shown to bioconcentrate in aquatic organisms.

Biomagnification of organolead compounds has not been found to occur. Depuration is relatively rapid, with half-life values of 30–45 hours for rainbow trout exposed to tetramethyl Pb. Tetraalkyl Pb compounds are more toxic than trialkyl Pb compounds, and ethyl forms are more toxic than methyl forms (Eisler 1988). Isolation of a *Pseudomonas aeruginosa* strain designated CHL004, which is able to remove Pb from solidified media and soil, has been reported (Vesper et al. 1996). The rate of uptake of Pb nitrate by CHL004 was very rapid initially and then decreased greatly.

5.4.2 Transformation and Degradation

As an element, Pb cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Pb will typically be found in compounds with oxygen and sulfur, and may undergo oxidation-reduction reactions under different environmental conditions. Under most environmental conditions, Pb will most likely exist in its Pb(II) oxidation state. Pb can be complexed by various ligands present in the environment (e.g., fulvic and humic acids). Despite forming complexes with organic matter, it is unlikely that it would be incorporated into organic compounds under environmental conditions. Transformations of Pb compounds that occur during their movement through the environment will be between various inorganic compounds.

Air. According to EPA (2014c), Pb accumulated on airborne mineral dusts can be transformed into different compounds during transport. It was also noted that Pb can accumulate on coarse particulate

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matter during transport in air and undergo chemical transformations. For example, Pb sulfate (PbSO_4), one of the main components of Pb-containing aerosols from coal combustion, can react with calcite (CaCO_3) in particulate matter to form various Pb carbonate compounds on the calcite surface. Another study included in the discussion noted that Pb levels in the PM_{10} fraction from dust storms collected in Israel were enriched with Pb at levels higher than those found in their source in the Sahara desert, suggesting that the dust samples accumulated Pb during transit between the Sahara desert and Israel (EPA 2014c).

Before the ban on sales of leaded gasoline, Pb particles were emitted to the atmosphere from automobile exhaust as Pb halides (mostly PbBrCl) and as double salts with ammonium halides (e.g., $2\text{PbBrCl} \cdot \text{NH}_4\text{Cl}$, $\text{Pb}_3[\text{PO}_4]_2$, and PbSO_4) (Biggins and Harrison 1979; Ter Haar and Bayard 1971). After 18 hours, approximately 75% of the bromine and 30–40% of the chlorine was released, and Pb carbonates, oxycarbonates, and oxides were produced. These Pb oxides are subject to further weathering to form additional carbonates and sulfates (Olson and Skogerboe 1975). Pb particles are emitted from mines and smelters primarily in the form of elemental Pb and Pb-sulfur compounds, PbSO_4 , $\text{PbO} \cdot \text{PbSO}_4$, and PbS (Corrin and Natusch 1977; EPA 1986b; Spear et al. 1998). The Pb emitted from the combustion of waste oil was found to be in the form of PbCl_2 , PbO , and elemental Pb (Pb^0) (Nerin et al. 1999). In the atmosphere, Pb exists primarily in the form of PbSO_4 and PbCO_3 (EPA 1986b).

While Pb is no longer added to gasoline for on-road use, the inorganic Pb degradation products of these organolead compounds may still be present in the environment. Based on the vapor pressure of tetraethyl Pb (0.26 mmHg at 25 °C) and tetramethyl Pb (26.0 mmHg at 20 °C), these two compounds exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). When exposed to sunlight, they decompose rapidly to trialkyl and dialkyl Pb compounds, and eventually to inorganic Pb oxides by a combination of direct photolysis, reaction with hydroxyl radicals, and reaction with ozone. The half-life of tetraethyl Pb in reactions with hydroxyl radicals during summer is approximately 5.7 hours, based on a rate constant of $6.8 \times 10^{-11} \text{ cm}^3/\text{molecule-second}$ (Nielsen et al. 1991). The half-life for tetramethyl Pb is about 65 hours, based on a rate constant of $5.9 \times 10^{-12} \text{ cm}^3/\text{molecule-second}$. In the winter, both compounds have half-lives of up to several days since the concentration of atmospheric hydroxyl radicals is lower than in summer months (DeJonghe and Adams 1986).

Water. The fate of Pb in water will be determined by the conditions of the water, including acidity (pH), ionic strength, oxidation-reduction potential, flow rate, and amount and composition of suspended materials (EPA 2014c). The pH of water is an important factor in determining the fate of Pb in water. At

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neutral to more basic pH, Pb will tend to be complexed, precipitated, or sorbed to suspended sediments in water (EPA 2014c). Pb will form compounds of low solubility with the major anions found in natural waters. The maximum solubility of Pb in hard water is about 30 µg/L at pH>5.4 and the maximum solubility of Pb in soft water is approximately 500 µg/L at pH>5.4 (EPA 1977). In the environment, the divalent form (Pb²⁺) is the stable ionic species of Pb. Hydroxide, carbonate, sulfide, and, more rarely, sulfate may act as solubility controls in precipitating Pb from water. At pH<5.4, the formation of Pb sulfate limits the concentration of soluble Pb in water, while at pH>5.4, the formation of Pb carbonates limits the amount of soluble Pb (EPA 1979). The relatively volatile organolead compound, tetramethyl Pb, may form as a result of biological alkylation of organic and inorganic Pb compounds by microorganisms in anaerobic lake sediments; however, if the water over the sediments is aerobic, volatilization of tetramethyl Pb from the sediments is not considered to be important because the tetramethyl Pb will be oxidized (EPA 1979).

The speciation of Pb was found to differ in fresh water and seawater. In fresh water, Pb may partially exist as the divalent cation (Pb²⁺) at pHs below 7.5, but complexes with dissolved carbonate to form insoluble PbCO₃ under alkaline conditions (Long and Angino 1977). Even small amounts of carbonate ions formed in the dissolution of atmospheric CO₂ are sufficient to keep Pb concentrations in rivers at the 500 µg/L solubility limit (EPA 1979). Pb chloride and Pb carbonate are the primary compounds formed in seawater (Long and Angino 1977). The speciation of Pb in water is also dependent on the presence of other ligands in water. Pb is known to form strong complexes with humic acid and other organic matter (Denaix et al. 2001; Gao et al. 1999; Guibaud et al. 2003). Pb-organic matter complexes are stable to a pH of 3 with the affinity increasing with increasing pH, but decreasing with increased water hardness (EPA 1979). In seawater, there is the presence of Pb complexed to Fe-Mn oxides, which is due to the content of these oxides in seawater (Elbaz-Poulichet et al. 1984). Sorption of Pb to polar particulate matter in fresh water and estuarine environments is an important process for the removal of Pb from these surface waters. The adsorption of Pb to organic matter, clay, and mineral surfaces, and coprecipitation and/or sorption by hydrous iron and manganese oxides increases with increasing pH (EPA 1979).

Sediment and Soil. Pb in its naturally-occurring mineral forms is a component of many soils in the United States. The speciation of Pb in soils is dependent upon the properties of the soil. In a calcareous soil, PbSO₄ and PbCO₃ were shown to account for <5% of the total Pb content, whereas in roadside dust, PbSO₄, elemental Pb, Pb₃O₄, PbO·PbSO₄, and 2PbCO₃·Pb(OH)₂ were present in significant quantities (Chaney et al. 1988). It was also reported that after adding 3,000–4,000 mg/kg of Pb in the form of

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PbSO₄, subsequent extractions revealed that the Pb sulfate was rapidly transformed to other Pb compounds in the soil (Chaney et al. 1988).

Nearly all forms of Pb that are released to soil from anthropogenic sources, such as elemental Pb, PbSO₄, PbCO₃, PbS, Pb(OH)₂, PbCrO₄, and PbClBr, are transformed by chemical and biotic processes to adsorbed forms in soil (Chaney et al. 1988). The transformation process involves the formation of Pb complexes with binding sites on clay minerals, humic acid and other organic matter, and hydrous iron oxides (Chaney et al. 1988; Chuan et al. 1996; Sauve et al. 1997). The ability of soils to bind Pb is dependent on soil pH and the cation exchange capacity of the soil components (e.g., hydrous iron oxides on clay and organic matter) (Chaney et al. 1988; EPA 1986b). Only a small fraction (0.1–1%) of Pb appears to remain water-soluble in soil (Khan and Frankland 1983). The solubility of Pb in soil is dependent on pH, being sparingly soluble at pH 8 and becoming more soluble as the pH approaches 5 (Chuan et al. 1996). Between pH 5 and 3.3, large increases in Pb solubility in soil are observed. These changes in Pb solubility appear to correlate with the pH-dependent adsorption and dissolution of Fe-Mn oxyhydroxides. In addition to pH, other factors that influence Pb solubility in soil are total Pb content and the concentrations of phosphate and carbonate in soils (Bradley and Cox 1988; Ge et al. 2000; Pardo et al. 1990; Sauve et al. 1997).

Large particles of elemental Pb (e.g., shot and bullet fragments) degrade from weathering processes (Cao et al. 2003a, 2003b). Weathering includes physical transformation of larger particles to smaller particles (particle dissolution), as well as oxidation of the particle surface (coating) to PbO₂, with subsequent further oxidation to carbonates, phosphates, and sulfates (Cao et al. 2003a, 2003b; Hardison et al. 2004; Hashimoto 2013; Lewis et al. 2010; Lin et al. 1995; Rooney et al. 2007; Vantenlon et al. 2005). Particle dissolution rates for shotgun pellets in soils have been estimated to range from 1 to 20 mg/g pellet/year, depending on soil type, precipitation, and vegetation cover (Jorgenson and Willems 1987; Takamatsu et al. 2010).

Since the ban on the use of leaded gasoline, atmospheric Pb deposition to soil has decreased considerably. However, the deposited organolead compounds and their transformation products remain in the soil. Limited data indicate that tetraethyl and tetramethyl Pb are converted into water-soluble Pb compounds in soil through microbial metabolism (Ou et al. 1994). Using an Arredondo fine sand from Florida (92% sand, 7% silt, 1% clay, 11.8 g/kg organic carbon, pH 5.5), tetraethyl Pb was shown to degrade sequentially to monoionic triethyl Pb, diionic diethyl Pb, and eventually Pb⁺² (Ou et al. 1994). Experiments were conducted using non-sterilized and autoclaved soil samples. The presence of

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monoionic triethyl Pb and diionic diethyl Pb was generally lower in the autoclaved samples, suggesting that both abiotic and biotic mechanisms are responsible for the degradation of tetraethyl Pb. At the end of a 28-day incubation period, no tetraethyl Pb was present in the soil; however, there were significant quantities of monoionic triethyl Pb and diionic diethyl Pb, which suggest that the degradation products are more persistent than the original species. Although tetraethyl and tetramethyl Pb are not expected to leach significantly through soil, their more water-soluble metabolites may be subject to leaching (EPA 1985a).

Pb content in plants is largely the result of atmospheric deposition. This is due to the strong retention of particulate matter on plant surfaces that is difficult to remove through washing (EPA 1977). Uptake of Pb into plant tissue appears to involve a combination of uptake from the leaf surface and uptake from roots, with the relative contribution of each pathway dependent on species and soil characteristics (Angelova et al. 2010; Bindler et al. 2008; Chrastny et al. 2010; Cui et al. 2007; Guyette et al. 1991; Hu and Ding 2009; Nwosu et al. 1995). Pb taken up by the root systems remains largely associated with root tissues (Comino et al. 2011; Businelli et al. 2011; Deng et al. 2004; Mellem et al. 2009; Murray et al. 2009; Nan and Cheng 2001; Sonmez et al. 2008; Wang et al. 2011). Translocation from roots to stem and leaf tissue has been shown to occur in some species (Peralta-Videa et al. 2009; Shaheen and Tsadilas 2009; Tamura et al. 2005; Wang et al. 2006; Zapryanova et al. 2010). Eventually, the Pb will be returned to soil when these plants decay unless they are harvested (to possibly enter the food chain) or removed.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to Pb depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of Pb in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on Pb levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-11 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-12.

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Table 5-11. Lowest Limit of Detection Based on Standards^a

Media	Detection limit	Reference
Air	1.5 ng/cm ² (XRF)	EPA, 1999, Method IO-3.3
	2.6 µg/sample	NIOSH 2017b, Method 7082
	6 µg/sample	NIOSH 1998, Method 7702
	0.02 µg/sample	NIOSH 1994c, Method 7105
	0.05 µg/sample	NIOSH 2016a, Method 7701
	0.062 µg/filter	NIOSH 2003c, Method 7300
	0.062 µg/filter	NIOSH 2003a, Method 7301
	0.023 µg/mL	NIOSH 2003b, Method 7303
	0.6 µg/sample	NIOSH 2014a, Method 7302
	1 µg/sample	NIOSH 2014b, Method 7304
	0.062 µg/sample	NIOSH 2015, Method 7306
	0.03 µg/mL	OSHA 2002, Method ID-121
	2.1 µg/sample	OSHA 2002, Method ID-125G
Drinking water	1.1 µg/L (ICP-AES)	EPA 2003 Method 200.5
	0.02 µg/L (ICP-MS)	EPA 1994f Method 200.8
Surface water and groundwater	0.07 µg/L	EPA 1997b
	2.4 µg/L (GFAA)	EPA 1997b
	0.28 µg/L (GFAA with preconcentration)	
	0.07 µg/L (ICP-MS)	
	0.05 µg/L (ICP-MS)	USGS 1989
	60 µg/L (ICP-OES)	
	1 µg/L (GFAA)	USGS 1993
	1.1 µg/L (AVICP-AES)	
	10 µg/L (ICP)	USGS 1989
	100 µg/L (total recoverable, FLAA)	
	1 µg/L (whole water recoverable, GFAA)	
	0.5 µg/L (dissolved in water by GFAA)	
	100µg/L (suspended recoverable, FLAA)	
	100 µg/L (dissolved, FLAA)	
Soil/sediment	0.6 µg/L (ICP-MS)	EPA 1994d
	0.7 µg/L (GFAA)	
	10 µg/L (ICP-AES)	
	0.15 µg/g (ICP-MS)	NOAA 1998
	0.2 µg/g (XRF)	
	0.2 µg/g (GF-AAS)	
	10 µg/g (FLAA)	USGS 1989

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Table 5-11. Lowest Limit of Detection Based on Standards^a

Media	Detection limit	Reference
Wipes	0.042 µg/wipe	NIOSH 2003d, Method 9102
	0.02 µg/cm ² for 100-cm ² area (FLAA or ICP);	NIOSH 1996a, Method 9100
	0.001 µg/cm ² for 100-cm ² area (GF-AAS)	
	Range: 5–15 µg/wipe sample	NIOSH 2003e, Method 9105

^aDetection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

AES = atomic emission spectroscopy; AVICP = axially viewed inductively coupled plasma; FLAA = flame atomic absorption; GFAA = graphite furnace atomic absorption; GF-AAS = graphite furnace-atomic absorption spectrometer; GRAV = gravimetry; ICP = inductively coupled plasma; MS = mass spectrometry; OES = optical emission spectrometry; Pb = lead; XRF = x-ray fluorescence

Table 5-12. Lead Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median ^a	Geometric mean ^a	Geometric standard deviation ^a	Number of quantitative measurements	NPL sites
Water (ppb)	75	118	13.8	1,452	659
Soil (ppb)	1,110,000	885,000	19.7	1,453	661
Air (ppbv)	0.194	0.286	32.3	85	51

^aConcentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Four national monitoring networks collect data on Pb concentrations in ambient air to report to the Air Quality System (AQS). State and local agencies carry out monitoring at state and local monitoring stations (SLAMS). These data are primarily used to evaluate compliance with the National Ambient Air Quality Standard (NAAQS) for Pb. Pb levels are also monitored in the Chemical Speciation Network (CSN), Interagency Monitoring of Protected Visual Environments (IMPROVE), and National Air Toxics Trends Station (NATTS) networks. Pb concentrations in air are measured in three particulate matter (PM) size fractions: total suspended particles (TSP), PM₁₀, and PM_{2.5}. The CSN and IMPROVE networks monitor Pb in PM_{2.5} and the NATTS network monitors Pb in PM₁₀. These networks are designed to meet different objectives than those of the Pb NAAQS monitoring network (EPA 2006, 2014c). EPA (2014c) analyzed data from these monitoring systems and presented data summaries for

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source-oriented (defined as near point sources and exceeded a defined emission threshold) and non-source-oriented Pb monitors across the United States for 2008–2010 (EPA 2014c). Maximum 3-month daily average Pb concentrations were calculated for non-source-oriented Pb-TSP monitors for 47 counties across the United States (1.5% of U.S. counties) and for source-oriented Pb-TSP monitors for 50 counties across the United States (1.6% of U.S. counties) during the period 2008–2010. Summaries of these analyses are presented in Table 5-13.

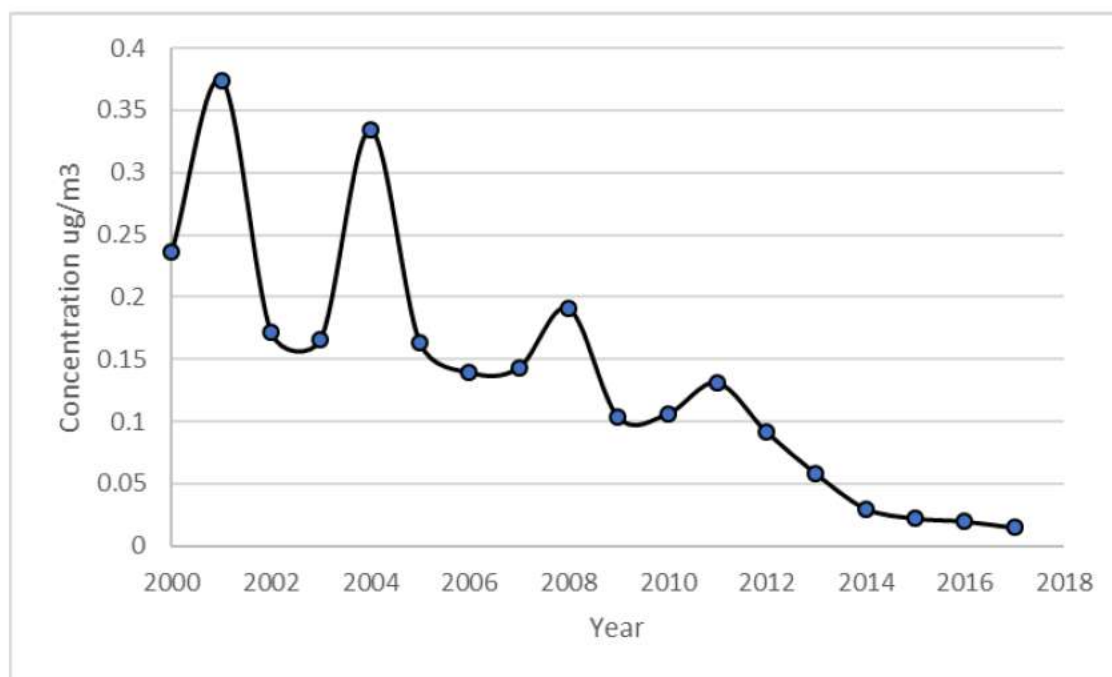
Table 5-13. Summary Data for Lead Monitors Across the United States, 2008–2010 ($\mu\text{g}/\text{m}^3$)

	Mean	Median	95 th %	99 th %	Maximum
Monthly (source-oriented)	0.20	0.063	0.86	1.6	4.4
Monthly (nonsource-oriented)	0.012	0.010	0.040	0.052	0.14

Source: EPA 2014c

Pb levels have been declining in the ambient air of the United States for several decades and according to the EPA, there has been approximately a 94% decrease since 2000 (EPA 2018a). Figure 5-3 shows the annual maximum 3-month average Pb level in the United States based upon data at 24 monitoring sites.

Figure 5-3. Annual Maximum 3-Month Average Representing the National Trend



Source: EPA 2018a

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Data compiled from the EPA AQS database from 2015 to 2018 were used to calculate the percentile distribution of arithmetic mean 3-month averages at locations across the United States. These data are summarized in Table 5-14.

Table 5-14. Percentile Distribution of Mean Lead (TSP) Concentrations ($\mu\text{g}/\text{m}^3$) Measured in Ambient Air at Locations Across the United States

Year	Percentile				Maximum
	25th	50th	75th	95th	
2015	0.0036	0.0090	0.0216	0.0753	0.1942
2016	0.0038	0.0093	0.0220	0.0782	0.1466
2017	0.0039	0.0080	0.0190	0.0756	0.2087
2018	0.0035	0.0090	0.0313	0.1248	0.5574

TSP = total suspended particles

Source: EPA 2018b

Pb in indoor air is related to Pb in housedust, and predominant sources are outdoor air and degraded Pb-based paint (EPA 2006). Smoking can also contribute to higher concentrations of Pb in indoor air. Pb concentrations in air and dust in the indoor environment were measured in residential homes as part of the National Human Exposure Assessment Survey (NHEXAS) in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin). Mean (± 1 SD) and median concentrations of Pb in indoor air from 213 residences were $15.2 \text{ ng}/\text{m}^3$ ($37.6 \text{ ng}/\text{m}^3$) and $6.17 \text{ ng}/\text{m}^3$, respectively, with a maximum value of $293.5 \text{ ng}/\text{m}^3$ (Bonanno et al. 2001). The median Pb concentration in outdoor air was $8.84 \text{ ng}/\text{m}^3$ (Clayton et al. 2002). Pb concentrations were higher in households where one or more residents smoked indoors (mean concentration of $21.8 \text{ ng}/\text{m}^3$) as compared to households with nonsmoking residents (mean concentration of $7.79 \text{ ng}/\text{m}^3$) (Bonanno et al. 2001). In dust collected from the living areas of 238 residences, the mean (± 1 SD) and median Pb concentrations were $467.4 \mu\text{g}/\text{g}$ ($2,100 \mu\text{g}/\text{g}$) and $131.6 \mu\text{g}/\text{g}$, respectively, with a maximum value of $30,578 \mu\text{g}/\text{g}$. Dust samples collected from window sills had mean (± 1 SD) and median Pb concentrations of $987 \mu\text{g}/\text{g}$ ($2,723 \mu\text{g}/\text{g}$) and $207.5 \mu\text{g}/\text{g}$, respectively, with a maximum value of $21,120 \mu\text{g}/\text{g}$. For both indoor air and dust measurements, higher concentrations of Pb were correlated with dilapidated and suburban homes. Dixon et al. (2009) analyzed children's exposures to residential dust Pb using data from the NHANES survey and associated demographics as well as smoking status to exposure levels. Children who resided in homes in which smoking occurred indoors had significantly ($p=0.015$) higher PbB levels than children who lived in homes of nonsmokers.

In another analysis of the NHEXAS EPA Region V data, Pellizzari et al. (1999) looked at potential differences in Pb concentrations in indoor air and personal air exposures between minorities (e.g., Hispanics and African-Americans) and nonminorities (e.g., Caucasian). Some differences were noted in the mean (± 1 SD) Pb concentrations between minorities of 57 ng/m^3 ($\pm 24 \text{ ng/m}^3$) and nonminorities of 22 ng/m^3 ($\pm 3.4 \text{ ng/m}^3$) in personal air exposures, although the differences were not significant ($p=0.147$). Similarly, differences were noted between minorities ($26 \pm 12 \text{ ng/m}^3$) and nonminorities ($13 \pm 2.6 \text{ ng/m}^3$) in indoor air, although these were also not significantly different ($p=0.266$). When the age of the home was considered in the analysis, it was found that Pb concentrations were significantly ($p=0.036$) higher in homes built before 1940 than in homes built between 1960 and 1979, with mean (± 1 SD) values of 46 ng/m^3 ($\pm 1.6 \text{ ng/m}^3$) and 13 ng/m^3 ($\pm 2.1 \text{ ng/m}^3$), respectively. The Pb concentrations measured in indoor air in homes built before 1940 were not significantly different from mean (± 1 SD) Pb concentrations of 22 ng/m^3 ($\pm 5.1 \text{ ng/m}^3$) and 23 ng/m^3 ($\pm 5.1 \text{ ng/m}^3$) measured in indoor air in homes built between 1940 and 1959 and between 1980 and 1995, respectively.

5.5.2 Water

Pb has been monitored in surface water, groundwater, and drinking water throughout the United States and other countries. The concentration of Pb in surface water is highly variable depending upon sources of pollution, Pb content of sediments, and characteristics of the system (pH, temperature, etc.). Pb concentrations in surface water are generally higher in urban areas than in rural areas (EPA 1982c), and Pb measured in natural or “pristine” surface waters may be due to anthropogenic input. Western Airborne Contaminants Assessment Project (WACAP) data collected at five U.S. National Parks showed median Pb levels in surface waters ranging from 0.006 to 0.075 $\mu\text{g/L}$ (EPA 2014c). The median Pb level in natural river water was 5 $\mu\text{g/L}$, with a range of 0.6–120 $\mu\text{g/L}$; however, lower Pb levels are to be expected after leaded gasoline was banned in 1985, which resulted in decreased rates of atmospheric deposition (Bowen et al. 1966; King et al. 2014). The National Academies of Science reported Pb concentration levels in surface water and groundwater (EPA 1986b). The mean Pb concentration level in surface water was 4 $\mu\text{g/L}$ with a range from below the detection limit to 890 $\mu\text{g/L}$ (EPA 2014c); concentrations $>100 \text{ } \mu\text{g/L}$ were observed near sources of urban runoff or industrial discharge. Mean levels of Pb in surface water measured at 50,000 surface water stations throughout the United States were 3.9 $\mu\text{g/L}$ (based on 39,490 occurrences) (Eckel and Jacob 1988). Using the EPA Storage and Retrieval (STORET) database, from January 1, 2005 to May 16, 2005, Pb had been detected in surface water in Washington, Utah at concentrations of 20.5 and 142 $\mu\text{g/L}$ and surface water from Salt Lake City, Utah at 7.75 $\mu\text{g/L}$ (EPA 2005b). Pb was not detected above the detection limits in 224 other surface water samples obtained

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from various locations in Utah and Iowa over the sampling period (EPA 2005b). Pb content in groundwater is driven largely by the surrounding bedrock geochemistry; Pb concentrations are generally low in groundwater and natural springs ranging from below the detection limit to 100 µg/L (EPA 2014c). A USGS study of groundwater in the United States from 2000 to 2016 concluded that <1% of measured Pb concentrations are >15 µg/L, but when high levels are detected, they are typically associated with geographic locations where the Pb solubility potentials (the amount of Pb that could dissolve before a Pb mineral precipitates out of solution) are naturally high (Jurgens et al. 2019). Pb levels in seawater are typically in the range of 0.001–0.036 µg/L in the open ocean and about 0.050–0.30 µg/L in coastal waters influenced by anthropogenic activity (Angel et al. 2016).

Urban storm water runoff is an important source of Pb entering receiving waterways. Sources of Pb in runoff can be contributed to substantial direct atmospheric deposition, as well as indirect release from building materials, soil, and road dust, and industrial discharge. Pb is found in building material (brick, concrete, painted and unpainted wood, roofing, and vinyl), and automotive sources (brakes, used oil), which contribute to runoff (Davis et al. 2001). The largest contributing sources were siding and roofing. Soto-Jiménez and Flegal (2009) evaluated the sources of Pb pollution in the Gulf of California, northwest Mexico by sampling urban and rural areas for Pb levels and isotope ratios. Urban street dust (157 µg/g), agricultural soils (29.0 µg/g), and surface estuary sediments (35.6 µg/g) were all higher than natural bedrock (16.0 µg/g). Isotopic ratios in rural and soil runoff samples were comparable to natural Pb containing bedrock. Pb concentrations in the suspended particulate matter were measured in sewage effluent (132 µg/g), agricultural effluent (29.3 µg/g), river runoff (7.3 µg/g), and estuary water (68.3 µg/g). Urban, street dust, and sewage showed contributions from automotive emissions from past leaded gasoline combustion.

Pb in drinking water can derive from source water contamination as described above, but the more common source of Pb in drinking water is from internal corrosion of water distribution system piping and plumbing. Internal corrosion of Pb service lines, Pb-based pipe solder, brass meters and plumbing fixtures, and dissolution of existing protective scales contribute directly to Pb levels in drinking water. The Lead and Copper Rule (LCR) was promulgated in 1991 with the purpose of protecting public health by minimizing Pb and copper levels in drinking water, primarily by reducing water corrosivity (EPA 2004). The LCR established a Pb action level (AL) of 15 µg/L and a maximum contaminant level goal (MCLG) of zero. The Pb action level is based on feasibility of public water systems to control corrosion in their distribution systems and is not a health benchmark for Pb in drinking water. The Pb action level is exceeded if the concentration of the 90th percentile first draw tap sample (collected after a minimum

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stagnation period of 6 hours from high risk sites) exceeds 15 µg/L (EPA 2016a). If the Pb AL is exceeded, the LCR can require public water systems to take steps to minimize the risk of Pb exposure that may include source water monitoring/treatment, public education, water quality monitoring, implementing corrosion control treatment, and Pb service line replacement. In October 2019, EPA proposed significant changes to the LCR (EPA 2019a). These changes include: (1) identify areas most in need of remediation of Pb service lines; (2) establish a trigger level of 10 µg/L for requiring corrosion control in drinking water systems that do not currently treat for corrosion; (3) require water system to replace Pb service lines; (4) increase sampling reliability by prohibiting pre-stagnation flushing and other methods; (5) require systems to notify customers of action level exceedance within 24 hours; and (6) protect children in schools by expanding testing at drinking water outlets.

Analyses done in support of the short-term revisions to the LCR at the beginning of the 21st century suggest that in 2003, <2% of public water systems serving >3,300 people exceeded the Pb action level of 15 µg/L (EPA 2007a). Additionally, a 2004 study conducted by the EPA on LCR compliance monitoring for public water systems serving >3,300 people indicated that <4% of those systems exceeded the Pb action level (Hill 2011). It is important to note that states were not required until 2002 to report 90th percentile Pb concentrations to the EPA unless those samples exceeded the Pb AL; therefore, it is difficult to accurately compare differences between tap water Pb levels prior to LCR implementation and immediately following LCR implementation with current nationwide Pb concentration levels (Hill 2011). Nevertheless, the EPA evaluated water sample data from 166 large public water systems (systems serving >50,000 people) that exceeded the Pb AL in 1992 and 1993 (Hill 2011). Of the large systems that exceeded the Pb AL in 1992–1993, only 15 of those systems continued to exceed the Pb AL between 2000 and 2004, and their associated average 90th percentile Pb concentration levels significantly decreased from 32 to 8.2 µg/L.

The amount of Pb contained in pipes and plumbing fittings has been strictly regulated since 1986. Section 1417 of the Safe Drinking Water Act (SDWA) was amended to ban the use of service lines, pipe fittings, pipe solder, and fixtures that are not “Pb free” (not more than 0.2% Pb for pipe solder and flux, and not more than 8% Pb for pipe fittings and service lines) and are connected to a public water system and intended to provide water for human consumption. The 1996 Amendment broadened this ban by limiting the amount of leaching of Pb from new plumbing, and an industry standard was established. In 2011, the Reduction of Lead in Drinking Water Act amended Section 1417, revising the existing SDWA definition of “Pb free” and getting rid of the leaching certification requirement. Implemented in 2014, the

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act reduced the allowable level of Pb by “not more than a weighted average of 0.25 percent Pb when used with respect to the wetted surfaces of pipes, pipe fittings, plumbing fittings and fixtures.”

According to EPA's National Public Water Systems Compliance Report for calendar year 2013 (EPA 2013), 73% of public water systems in the United States, serving approximately 77% of the population, had no significant reported violations of any type. Significant violations include all violations of health-based standards, including violations of the maximum contaminant levels, treatment technique requirements, and significant monitoring and reporting requirements. In 2013, 7% of public water systems had no reported violations of health-based standards, and 5% of all health-based standard violations were LCR violations.

In the spring of 2014, the source of drinking water in the city of Flint, Michigan was switched from treated water obtained from Lake Huron to the Flint River. However, the treated water from the Flint River was more corrosive and did not contain corrosion inhibitors, which resulted in Pb leaching from the city's aging service lines. Sampling data conducted in August of 2015 showed that the 90th percentile concentration of Pb in first-draw drinking water was 26.8 µg/L for 268 samples of tap water, which far exceeded the EPA AL of 15 µg/L (Pieper et al. 2018). In response to the high Pb levels in Flint drinking water, the city reconnected to the DWSD in October of 2015. By August of 2017, the 90th percentile concentration of Pb in first-draw tap water was 7.9 µg/L (Pieper et al. 2018).

5.5.3 Sediment and Soil

Pb is a naturally occurring metal found in the earth's crust at about 15–20 mg/kg (Goyer 2001). However, the concentration of Pb in the top layers of soil varies widely due to deposition and accumulation of atmospheric particulates from anthropogenic sources. The concentration of soil Pb generally decreases as distance from contaminating sources increases. The estimated Pb levels in the upper layer of soil beside roadways are typically 30–2,000 µg/g higher than natural levels, although these levels drop exponentially up to 25 m from the roadway (EPA 1986b). Soil adjacent to a smelter in Missouri had Pb levels in excess of 60,000 µg/g (Palmer and Kucera 1980). Soils adjacent to houses with exterior Pb-based paints have reported Pb levels >10,000 µg/g (EPA 1986b). As a result of Pb reactions with the soil, extractable Pb in surface soil samples (0–5 cm depth) from an agricultural area near a car battery manufacturing plant (taken at 0.3 km from the source) decreased from 117 to 1 µg/g within 1 year after the plant stopped operating (Schalscha et al. 1987). Soil collected by scraping the top 2.5 cm of soil surface near homes and streetside in Louisiana and Minnesota contained median Pb concentrations of >840 µg/g in New

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Orleans and 265 µg/g in Minneapolis. In contrast, the small towns of Natchitoches, Louisiana, and Rochester, Minnesota had soil Pb concentrations of <50 and 58 µg/g, respectively. These data suggest that Pb-contaminated soil is a major source of Pb exposure in urban areas (Mielke 1993). As would be expected, soils in elementary school properties were also found to have the same pattern of Pb levels as the soils in the surrounding residences. Pb concentrations in soils collected from inner-city schools in New Orleans were higher (median concentration of 96.5 µg/g) than soils collected from mid-city (30.0 µg/g) and outer-city (16.4 µg/g) elementary schools (Higgs et al. 1999).

The former use of Pb in paints, particularly in older structures, is also a source of Pb in soil and within homes. Mielke and Gonzales (2008) reported median Pb concentrations of 76,603 mg/kg (464–317,151 mg/kg) and 416 mg/kg (24–63,313 mg/kg) for exterior and interior paints, respectively, in 40 paint chip samples collected from homes in metropolitan New Orleans. The authors noted that the age of the house is often used as a surrogate for the amount of Pb in paints; the mid-1920s being the peak use of leaded paint with declines until 1978. Demolition and renovation of buildings where leaded paint was used can result in transport of Pb to soil surrounding the building as well as indoor dust that contains Pb.

Pb concentrations were measured in residential transects through Lubbock, Texas. Pb concentrations through the city showed a trend of decreasing Pb concentrations with increasing distance from the city center, which also paralleled a decrease in the property age. The highest Pb concentrations in the city center were 90.0–174.0 mg/kg, with a median of 35.4 mg/kg, and decreased out to the farther part of the residential transect to 6.0–9.0 mg/kg. The highest concentrations outside city development were 4.9 mg/kg (Brown et al. 2008).

Studies conducted in Maryland and Minnesota indicate that within large, light-industrial, urban settings such as Baltimore, the highest soil Pb levels generally occur near inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1984, 1989) and that the amount of Pb in the soil is correlated with the size of the city (Mielke 1991). In 1981, soil Pb levels in the Minneapolis/St. Paul inner-city area were 60 times higher (423 µg/g) than levels found in rural Minnesota (6.7 µg/g), with almost all the increase (95%) resulting from the combustion of leaded gasoline. A study conducted in Minneapolis, Minnesota, after the Pb content of gasoline had been significantly reduced, found that median soil Pb levels taken from the foundations of homes, in yards, and adjacent to the street were 700, 210, and 160 µg/g, respectively; median soil Pb concentrations in comparable samples from the smaller city of Rochester, Minnesota, did not exceed 100 µg/g at any location tested (Mielke et al. 1989). The Minneapolis data suggested that average Pb levels were elevated in soil samples taken from the

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foundations of homes, but that Pb levels were low ($<50 \mu\text{g/g}$) in areas where children could be expected to play, such as parks that were located away from traffic, but were higher in play areas around private residences. Soil samples taken from around the foundations of homes with painted exteriors had the highest Pb levels (mean concentrations of $522 \mu\text{g/g}$), but levels around homes composed of brick or stucco were significantly lower (mean concentration $158 \mu\text{g/g}$) (Schmitt et al. 1988). Severely contaminated soils (levels as high as $20,136 \mu\text{g/g}$) were located near house foundations adjacent to private dwellings with exterior Pb-based paint. Elevated soil Pb concentrations were found in larger urban areas, with 27, 26, 32, and 42% of the soil samples exceeding $300 \mu\text{g/g}$ Pb in Duluth, inner-city North Minneapolis, inner-city St. Paul, and inner-city South Minneapolis, respectively. Only 5% of the soil samples taken from the smaller urban areas of Rochester and St. Cloud, Minnesota, had Pb levels $>150 \mu\text{g/g}$. It has been suggested that the higher Pb levels associated with soils taken from around painted homes in the inner city are the result of greater atmospheric Pb content, resulting from the burning of leaded gasoline in cars and the washdown of building surfaces to which the small Pb particles adhere by rain (Mielke et al. 1989). A state-wide Minnesota study concluded that exterior Pb-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences and that aerosol Pb accounted for virtually all of the contamination found in soils removed from the influence of Pb-based paint. Contamination due to Pb-based paint was found to be “highly concentrated over a limited area, while contamination due to aerosol Pb was found to be less concentrated, but more widespread” (Schmitt et al. 1988).

Pb was analyzed in dust wipes and soil samples from 67 public housing projects containing 487 dwelling units across the United States (Succop et al. 2001). A total of 5,906 dust wipes and 1,222 soil samples were included in the data set. The median soil levels were 194 ppm near the foundation, 177 ppm near the walkways, and 145 ppm elsewhere in the yard. The maximum level, 3,900 ppm, was found in a foundation sample. Median dust Pb loading ($\mu\text{g m}^{-2}$) from kitchens, living rooms, and two children’s bedrooms were 151 (5th–95th percentile range: 22, 674), 936 (86, 10,190), and 8,560 (818, 313,000) for floor window sills and window troughs, respectively. Thirteen percent of the floor samples and 30% of the window sill samples from the rooms exceeded the HUD Interim Dust Lead Standards of 431 and $2,690 \mu\text{g m}^{-2}$ for floor and window sill samples, respectively.

5.5.4 Paint

Weathering and deterioration of Pb-based paint can contribute to the Pb content of dust and soil (Clark et al. 2004; Hunt et al. 1993; Jaeger et al. 1998; Lucas et al. 2014; Marcus and Elias 1995). A soil Pb study

in Minneapolis, Minnesota, found that soil samples taken from around the foundations of homes with painted exteriors had a mean concentration of 522 µg/g, while soil samples taken from around the foundations of brick or stucco had a mean concentration of 158 µg/g (Schmitt et al. 1988). Pb-based paint, removed from surfaces by burning (gas torch or hot air gun), scraping, or sanding have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. A 2006 survey of U.S. housing stock estimated that 35% of 106 million housing units contained Pb-based paint and that approximately 20% of houses contained deteriorating Pb-based paint (HUD 2011).

5.5.5 Other Media

Pb has been detected in a variety of foods and spices (Lin et al. 2010). Pb may be introduced into food through uptake from soil into plants or atmospheric deposition onto plant surfaces, during transport to market, processing, and kitchen preparation (EPA 1986b). The ban on leaded gasoline as well as the use of welded (non-soldered) food cans during the 1980s are largely responsible for the decreases in levels of Pb in the U.S. diet beginning in the 1980s (FDA 2006). The FDA analyzed samples of foods commonly eaten by toddlers and infants for Pb and noted that levels of Pb in infant and toddler foods, on average, are relatively low (FDA 2016a). These results are summarized in Table 5-15. Selected data from the 2006–2011 FDA Total Diet Study Market Baskets are presented in Table 5-16 (FDA 2016b). Mean Pb levels in dairy products (e.g., milk, cheese, ice cream, cream, yogurt) were generally low or below the detection limit. The dairy product category with the highest Pb level was for low-fat fruit-flavored yogurt, with a mean concentration of 0.002 mg/kg for 24 analyses. Mean concentrations of Pb in fruits and vegetable were also generally low, with the highest concentrations in raisins (0.005 mg/kg), spinach (0.004 mg/kg), and lettuce (0.004 mg/kg). Mean concentration of Pb in baby foods ranged from not detected to 0.013 mg/kg. The highest levels reported were found in sweet potatoes (0.013 mg/kg), arrowroot cookies (0.012 mg/kg), grape juice (0.011 mg/kg), teething biscuits (0.008 mg/kg), and apple-cherry juice (0.008 mg/kg). Based on a multimedia Pb exposure modeling analysis for children 1–5 years old, below the 70th percentile of PbB in the general U.S. population, dietary intake was a major background exposure pathway (Zartarian et al. 2017)

Table 5-15. Lead Levels in Foods Commonly Eaten by Toddlers and Infants

Product category	Average ^a (range) (µg/kg)	Number of samples
Cereal, infant/toddler (rice)	15.6 (5.0–82.0)	76
Cereal, infant/toddler (multigrain)	7.2 (6.0–8.0)	6
Cereal, infant/toddler (non-rice)	4.8 (0.4–17.0)	30

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Table 5-15. Lead Levels in Foods Commonly Eaten by Toddlers and Infants

Product category	Average ^a (range) (µg/kg)	Number of samples
Apples ^b	3.3	10
Cereal, oat ring	7.8 (3.3–16.4)	30
Grapes	3.7 (3.3–7.6)	10
Juice, grape	5.6 (0.3–41.3)	30
Juice boxes and pouches	3.3 (0.3–17.0)	40
Peanut butter	5.3 (3.3–45.2)	29
Quinoa	22.2 (0.4–98.0)	30
Raisins	18.1 (1.8–151)	23
Stage 2 toddler foods	5.2 (1.0–22.2)	35
Teething biscuits	12.0 (2.0–131)	27
Toddler puffs	19.1 (3.3–91.0)	31

^aThe average concentration reported for each product category was calculated using all values. For those samples with results below the detection limit, half of the detection limit was used to calculate the average.

^bAll of the apple samples were below the limit of detection.

Source: FDA 2016a

Table 5-16. Selected Mean Lead Concentrations in Food from the FDA Total Diet Study

Food	Mean (range) (mg/kg) ^a	Number of analyses	Number <LOD	LOD (mg/kg)
Syrup, chocolate	0.016 (0–0.027)	24	1	0.007
Apricots, canned in heavy/light syrup	0.015 (0–0.036)	24	1	0.007
Baby food, sweet potatoes	0.013 (0–0.034)	24	5	0.007
Peach, canned in light/medium syrup	0.013 (0–0.038)	24	2	0.007
Candy bar, milk chocolate, plain	0.013 (0–0.027)	24	5	0.01
Baby food, arrowroot cookies	0.012 (0–0.031)	24	9	0.01
Sweet potatoes, canned	0.012 (0–0.018)	24	2	0.007
Shrimp, boiled	0.012 (0–0.18)	24	18	0.01
Baby food, juice, grape	0.011 (0–0.02)	24	1	0.004
Fruit cocktail, canned in light syrup	0.011 (0–0.025)	24	4	0.007
Brownie	0.01 (0–0.032)	24	5	0.007

^aNote: 1 mg/kg = 1,000 µg/kg.

FDA = U.S. Food and Drug Administration; LOD = limit of detection

Source: FDA 2016b

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The U.S. Fish and Wildlife Service reported the concentrations of metals in a total of 315 composite samples of whole fish sampled from 109 stations nationwide from late 1994 to early 1995. For Pb, the geometric mean, maximum, and 85th percentile concentrations ($\mu\text{g/g}$ wet weight) were 0.11, 4.88, and 0.22, respectively. The mean concentration of Pb was significantly lower than in the 1980–1981 survey. Pb concentrations in fish have declined steadily from 1976 to 1984, suggesting that reductions of leaded gasoline and controls on mining and industrial discharges have reduced Pb in the aquatic environment (Schmitt and Brumbaugh 1990).

In order to reduce Pb exposure from consumption of Pb-contaminated fish and shellfish, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish and shellfish species from certain water bodies where Pb concentrations in fish and shellfish tissues exceed the human health level of concern. This level of concern is set by individual state agencies and used to issue advisories recommending no consumption, or restricted consumption, of contaminated fish and shellfish from certain waterbody types (e.g., lakes and/or rivers). In 1995, the EPA Office of Water issued guidance to states on sampling and analysis procedures to use in assessing the health risks from consuming locally caught fish and shellfish. The risk assessment method proposed by EPA was specifically designed to assist states in developing fish consumption advisories for recreational and subsistence fishers (EPA 1995a). These two groups within the general population consume larger quantities of fish and shellfish than the general population and frequently fish the same water bodies routinely. Because of this, these populations are at greater risk of exposure to Pb and other chemical contaminants if the waters they fish are contaminated. In 2007, eight advisories restricting the consumption of Pb-contaminated fish and shellfish were in effect in five states (Hawaii, Idaho, Washington, Kansas, and Missouri) and one territory (American Samoa) (EPA 2007b).

Elevated levels of Pb in the blood of cattle grazing near a Pb smelter have been reported, although no implications regarding Pb in beef were made. The mean Pb levels for the herd were highest near the smelter and decreased with distance. Ingestion of soil along with the forage was thought to be a large source of additional metal (Neuman and Dollhopf 1992). Evidence has also been shown for transfer of Pb to milk and edible tissue in cattle poisoned by licking the remains of storage batteries burned and left in a pasture (Oskarsson et al. 1992). Levels of Pb in muscle of acutely sick cows that were slaughtered ranged from 0.23 to 0.5 mg/kg (wet weight basis). Normal Pb levels in bovine meat from Swedish farms are <0.005 mg/kg. For eight cows that were less exposed, levels of Pb in milk taken 2 weeks after the exposure were 0.08 ± 0.04 mg/kg. The highest Pb level found in the milk of eight cows studied for 18 weeks was 0.22 mg/kg. Pb in most milk samples decreased to values <0.03 mg/kg 6 weeks after

exposure. Two affected cows delivered a calf at 35 and 38 weeks after the exposure. There was a high Pb level in the blood of the cows at the time of delivery, which suggests mobilization of Pb in connection with the latter stages of gestation and delivery. Pb levels in colostrum were increased as compared to mature milk samples taken 18 weeks after exposure. The concentration of Pb in milk produced after delivery decreased rapidly with time and was almost down to the limit of detection in mature milk.

In a survey, 324 multivitamin-mineral products were analyzed for Pb content (Mindak et al. 2008). Estimates of Pb exposure from these products were derived for four groups summarized in Table 5-17. The overall median value for Pb exposure was 0.576 µg/day. Five samples would have provided exposures that exceeded 4 µg/day. The authors reported that the estimates of Pb exposures were below the provisional total tolerable intake levels for the four population groups (Mindak et al. 2008). Twenty-one elements, including Pb, were analyzed in various botanical and dietary supplements; Pb concentrations ranged from not detected to 4.21 µg/g. None of the products analyzed would result in a maximum exposure that exceeds a tolerable level of exposure (Avula et al. 2010).

Table 5-17. Estimated Median and Maximum Lead Exposures

Population group	Median (µg/day)	Maximum (µg/day)
Young children (0–6 years)	0.123	2.88
Older children (7+ years)	0.356	1.78
Pregnant or lactating women	0.845	8.97
Adult women	0.842	4.92

Source: Adapted with permission from Mindak et al. (2008), American Chemical Society.

Many non-Western folk remedies used to treat diarrhea or other ailments may contain substantial amounts of Pb. Examples of these include: Alarcon, Ghasard, Alkohl, Greta, Azarcon, Liga, Bali Goli, Pay-loo-ah, Coral, and Rueda. In addition, an adult case of Pb poisoning was attributed to an Asian remedy for menstrual cramps known as Koo Sar. The pills contained Pb at levels as high as 12 ppm (CDC 1998). The source of the Pb was thought to be in the red dye used to color the pills. Pb was the most common heavy metal contaminant/adulterant found in samples (n=54) of Asian traditional remedies available at health food stores and Asian groceries in Florida, New York, and New Jersey (Garvey et al. 2001). Sixty percent of the remedies tested would give a daily dose of Pb in excess of 300 mg when taken according to labeling instructions. Pb poisoning has been caused by ingestion of a Chinese herbal medicine to which metallic Pb was added to increase its weight and sales price (Wu et al. 1996). Ayurveda is a traditional form of medicine practiced in India and other South Asian countries; the medications used often contain herbs, minerals, metals, or animal products and are made in standardized

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and nonstandardized formulations (CDC 2004b). CDC (1998, 2002b) reported cases of elevated PbBs in children after consuming candy from Mexico or using various folk remedies. Elevated PbBs were reported in two 7-year-old children in Rhode Island. A sample of litargirio, which was used as an antiperspirant/deodorant, found in the home contained 79% Pb (CDC 2005).

During 2011–2012, six cases of Pb poisoning were associated with the use of 10 oral Ayurvedic medications made in India. Pb concentrations in these medications were as high as 2.4%. Blood Pb levels of these women ranged from 16 to 64 µg/dL (CDC 2012c). In 2004–2012, the New York City Department of Health and Mental Hygiene identified 22 oral medications, supplements, or remedies containing high levels of heavy metals, including Pb (Table 5-18).

Table 5-18. Lead Content in Ayurvedic Medications and Other Health Remedies

Product	Country where manufactured	Country where purchased	Lead content (ppm)
Calabash Chalk (Nzu)	Unknown	United States	6.6
Emperor's Tea Pill (concentrated)	China	United States	5,400
Garbha Chintamani Ras (Vrihat) (Swarna Yukt)	India	India	120
Garbha Dharak Yog	India	India	110
Garbhapal Ras	India	India	22,000
Garbhapal Ras	India	United States	15,000
Hepatico Extract (concentrated)	China	United States	5,900
Jambrulin	India	United States	243,000
Kankayan Bati (Gulma)	India	United States	12
Lakshmvilash Ras (Nardiya)	India	United States	260
Laxmana Louh	India	India	180
Maha Sudarshan	India	United States	41
Mahashakti Rasayan	India	India	9,400
Mahayogaraj Guggulu (enriched with silver)	India	United States	47,000
Ovarin	India	India	24,000
Pigmento	India	India	7.3
Pregnita	India	India	12,000
Sorin	India	India	46,707
Tierra Santa	Mexico	United States	13
Vasant Kusumakar Ras (with Gold and Pearl)	India	India	29
Vatvidhwansan Ras	India	United States	20,000
Vita Breath	United States	United States	1,100

Source: CDC 2012c

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A study was conducted in an urban neighborhood in Chicago in order to gauge the levels of Pb in an array of fruits, vegetables, and herbs (Finster et al. 2004). The soil Pb concentrations where the plants were sampled varied from 27 to 4,580 ppm (median 800 ppm, geometric mean 639 ppm). Detectable Pb levels in the edible fruit, vegetables, and herbs sampled ranged from 11 to 81 ppm. Only one fruiting vegetable (cucumber 81 ppm) among the 52 sampled had detectable levels of Pb in the edible portion. However, 12 of the 31 leafy vegetables and herbs sampled contained Pb in the edible shoot part of the plant (range, 11–60 ppm). The Pb concentrations in the four samples of root vegetables ranged from 10 to 21 ppm. No significant correlation was found between the Pb concentrations in the edible portion of plant and the soil Pb level.

Pb may leach from Pb crystal decanters and glasses into the liquids they contain. Port wine that contained an initial concentration of 89 µg/L Pb was stored for 4 months in crystal decanters containing up to 32% Pb oxide. At the end of 4 months, Pb concentrations in the port were 5,331, 3,061, and 2,162 µg/L in decanters containing 32, 32, and 24% Pb oxide, respectively. Pb was also found to elute from Pb crystal wine glasses within minutes. Mean Pb concentrations in wine contained in 12 glasses rose from 33 µg/L initially to 68, 81, 92, and 99 µg/L after 1, 2, 3, and 4 hours, respectively (Graziano and Blum 1991).

Hair dyes and some cosmetics may contain Pb compounds (Cohen and Roe 1991). Hair dyes formulated with Pb acetate may have Pb concentrations 3–10 times the allowable concentration in paint. Measured Pb concentrations of 2,300–6,000 µg of Pb/gram of product have been reported (Mielke et al. 1997). Pb acetate is soluble in water and easily transferred to hands and other surfaces during and following application of a hair dye product. Measurements of 150–700 µg of Pb on each hand following application have been reported (Mielke et al. 1997). In addition to transfer of Pb to the hand-to-mouth pathway of the person applying the product, Pb can be transferred to any other surface (comb, hair dryer, outside of product container, counter top, etc.) that comes into contact with the product. It is also on the hair that it is applied to and the hands applying it. Objects coming into contact with hair dyed with a Pb-containing product also become contaminated. A dry hand passed through dry hair dyed with a Pb-containing product in cream form was been shown to pick up about 786 µg of Pb. A dry hand passed through dry hair dyed using foam or liquid Pb-containing hair dye products picked up less Pb: 69 µg/hand for foam products and 73 µg/hand for liquid products (Mielke et al. 1997). An elevated PbB (12 µg/dL) in an infant was observed after the use of tiro, a Nigerian eye cosmetic applied to the infant's eyes (CDC 2012a). Elevated PbBs (27.0 and 33.5 µg/dL) were reported in two young children in New Mexico after the use of kajal, a cosmetic imported from Afghanistan, that was applied to the children's eyelids. The

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kajal was reported to contain 54% Pb (CDC 2013). Sindoor, a cosmetic and cultural/religious powder used in Hindu cultures, has been found to contain very high amounts of Pb (Lin et al. 2010).

Cases of Pb poisoning have been related to less common sources of exposure. Illicit "moonshine" whiskey made in stills composed of Pb-soldered parts (e.g., truck radiators) may contain high levels of Pb. Detectable levels of Pb with a maximum concentration of 5.3 mg/L were found in 7 of 12 samples of Georgia moonshine whiskey (Gerhardt et al. 1980). Of the 115 suspected moonshine samples seized by local law enforcement between 1995 and 2001 and analyzed by the Bureau of Alcohol, Tobacco, and Firearms, 33 samples (28.7%) contained Pb levels $>300 \mu\text{g/dL}$. The median and maximum levels were 44.0 and 53,200 $\mu\text{g/dL}$, respectively (Parramore et al. 2001).

Firing of Pb ammunition may result in exposure to Pb aerosols and dusts generated during gun or rifle discharge at levels up to $1,000 \mu\text{g/m}^3$ (EPA 1985c), from Pb pellets ingested by or imbedded in animals that are used as food sources, and from Pb pellets or fragments imbedded in humans from shooting incidents (see Appendix C, Ingestion of Lead Debris). Exposures to airborne Pb dust from firearm discharge in indoor shooting ranges has been shown to result in increases in PbBs that are 1.5–2 times higher than preexposure concentrations (Greenberg and Hamilton 1999; Gulson et al. 2002). However, the use of copper-jacketed bullets, nonlead primers, and well-ventilated indoor firing ranges lessen the impact of airborne Pb on blood Pb levels (Gulson et al. 2002).

A Pb poisoning hazard for young children exists in imported vinyl miniblinds that had Pb added to stabilize the plastic. Over time, the plastic deteriorates to produce Pb dust that can be ingested when the blinds are touched by children, who then put their hands in their mouths (CPSC 1996). The U.S. Consumer Product Safety Commission (CPSC) has requested that manufacturers change the manufacturing process to eliminate the Pb. As a consequence, vinyl miniblinds should now be Pb-free. The CPSC recommends that consumers with young children remove old vinyl miniblinds from their homes and replace them with new miniblinds made without added Pb or with alternative window coverings.

Inexpensive metallic jewelry items specifically intended for children and teenagers have been shown to contain varying levels of Pb (Maas et al. 2005). A total of 311 chemical assays conducted using 285 jewelry items purchased in 20 different stores in California revealed that a considerable amount of Pb was added to the items, presumably to increase their weight or to impart some type of metallic coating to the surface of the item. The mean weight percentage of Pb for all 311 assays was 30.6%. Of the

311 samples tested, 169 contained at least 3% Pb by weight in at least one portion of the jewelry piece and 123 of the samples were found to contain >50% Pb by weight (Maas et al. 2005). In addition, 62 pieces of the purchased jewelry were tested for surface levels of Pb that could potentially be transferred dermally through the routine handling of these pieces. Using standard laboratory wipes, the surface of the jewelry pieces were wiped for a total of 20 seconds and subsequently analyzed for Pb content. Mean Pb levels in the wipes ranged from 0.06 to 541.97 µg. The authors characterized the potential Pb exposure from these dermal transfer experiments as either low exposure (<1 µg of Pb transferred to the laboratory wipe), moderate exposure (1–10 µg of Pb transferred to the laboratory wipe), high exposure (10–50 µg of Pb transferred to the laboratory wipe), and very high exposure (>50 µg of Pb transferred to the laboratory wipe). Approximately 35% of the 62 pieces tested were characterized as having low exposure, 48% were characterized as moderate exposure, 11% were characterized as high exposure, and 5% were characterized as very high exposure (Maas et al. 2005).

5.6 GENERAL POPULATION EXPOSURE

Measurements of Pb in blood, urine, and tissues (postmortem) have been used to assess exposures of individuals to Pb. Table 5-19 shows the lowest limit of detections that are achieved by analytical analysis of blood, urine and tissues.

Table 5-19. Lowest Limit of Detection Based on Standards ^a		
Media	Detection limit	Reference
Whole blood/urine/tissue	0.05 µg Pb/g blood or mL urine	NIOSH 1994b, Method 8003
	1 µg/100 g blood; 0.2 µg/g tissue	NIOSH 1994a, Method 8005
Animal tissue	0.1 µg/g (ICP-MS or GFAA)	NOAA 1998

^aDetection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

GFAA = graphite furnace atomic absorption; ICP-MS = inductively coupled plasma-mass spectrometry

Prior to the 1980s, aerolized Pb emissions from the use of leaded gasoline was the main source of Pb exposure for the general U.S. population. Aerolized Pb can be either inhaled or ingested after deposition on surfaces and food crops. Adult Pb exposures tend to be limited to occupational or recreational sources. For children, the primary source of Pb exposure is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (Bornschein et al. 1986; CDC 2009; Dixon et al. 2009; Egeghy et al. 2005; EPA 1996c; Garavan et al. 2008; Gulson et al. 2009;

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Lanphear and Roghmann 1997; Lanphear et al. 1998a; Lewin et al. 1999; Malcoe et al. 2002; Mielke et al. 2007; Succop et al. 1998; Von Lindern et al. 2003, 2016; Zahran et al. 2013). Young children are particularly vulnerable to Pb exposure because of hand-to-mouth activity, which contributes to ingestion of Pb in surface dusts. Pb in the fine particle fraction of surface dusts ($<150\text{ }\mu\text{m}$) readily adheres to the skin surface, from which it can be inadvertently ingested from hand-to-mouth activity (Choate et al. 2006a, 2006b; Clausen et al. 1987; Davis and Mirick 2006; Davis et al. 1990; Siciliano et al. 2009; Yamamoto et al. 2006). Several studies have attempted to quantify soil and dust ingestion in children (Chien et al. 2017; Ozkaynak et al. 2011; Sedman et al. 1994; Stanek et al. 2012; Von Lindern et al. 2016; Wilson et al. 2013) and adults (Calabrese et al. 1990; Doyle et al. 2012; Irvine et al. 2014; Stanek et al. 1997).

Although air Pb can be a direct pathway of exposure in children, it can also be an indirect pathway from its effect on Pb concentration in surface dusts (Brunekreef 1984; Hayes et al. 1994; Hilts 2003; Rabinowitz et al. 1985; Schnaas et al. 2004; Schwartz and Pitcher 1989; Tripathi et al. 2001). Second-hand smoke may also contribute to increased Pb exposure (Apostolou et al. 2012; Mannino et al. 2003; Richter et al. 2013). Dietary sources of Pb can originate from direct or indirect transfer of atmospheric Pb emissions to secondary media such as water, food crops, game, and fish. Pb in the maternal system can also be transferred to the fetus during gestation and to the nursing infant (EPA 2014c).

Several studies provided data on Pb levels in food, with which dietary intakes of Pb for the general population in the United States have been estimated (FDA 2016a, 2016b). An analysis of individual food intakes and PbB from NHANES (2006–2008) estimated that diet explained approximately 2.9% of the variations of PbB in children and 1.6% in adults (Davis et al. 2014). A randomized survey of 250 individuals (adults and children) from the Midwest United States conducted over the period 1995–1997 estimated average dietary Pb intake to be approximately $10\text{ }\mu\text{g/day}$ (Clayton et al. 1999). The EPA has estimated mean dietary Pb intakes in children ages 6–84 months to be approximately $2\text{ }\mu\text{g/day}$ (EPA 2014c). The ban on the use of welded (non-soldered) food cans during the 1980s has resulted in a decrease in Pb exposure from foods (FDA 2006). In recent surveys, the mean Pb levels in dairy products (e.g., milk, cheese, ice cream, cream, yogurt) were generally low or below the detection limit. Mean concentrations of Pb in fruits and vegetables were also generally low. Mean concentration of Pb in baby foods ranged from not detected to 0.013 mg/kg . Possible sources of Pb in food samples include introduction during processing or preparation with drinking water contaminated with Pb, deposition of Pb onto raw materials for each food, and Pb exposure in livestock that produce dairy or meat ingredients (EPA 2014c). Pb has also been reported in home-prepared reconstituted infant formula. Although, at one

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time, use of Pb solder in formula containers contributed to PbB from formula consumption (Ryu et al. 1983), this practice was phased out after 1970 in the United States and subsequently banned (FDA 1995). However, tap water remains a potential source of Pb in home-prepared formula at locations where tap water Pb concentrations are elevated. In a study conducted in the Boston area in 1997, 2 of 40 samples of home-prepared formula had Pb concentrations $>15 \mu\text{g/L}$. In both cases, the reconstituted formula had been prepared using cold tap water run for 5–30 seconds, drawn from the plumbing of houses >20 years old. Pb-containing ceramic ware used in food preparation has also been associated with childhood Pb exposure in children of Hispanic ethnicity in San Diego County, California. One study (Gersberg et al. 1997) used the IEUBK Model to determine that dietary Pb exposure from beans prepared in Mexican ceramic bean pots may account for a major fraction of blood Pb burden in children whose families use such ceramic ware.

The main source of Pb in drinking water is from the corrosion of Pb service lines, which are pipes constructed of pure Pb that connect the water distribution main to a building's internal plumbing. Other common sources of Pb in drinking water are exposed leaded solder or corroded fixtures containing Pb (EPA 2016a). While Pb was restricted to no more than 8% in plumbing materials in 1986, older homes and neighborhoods may still contain Pb service lines, Pb connections, Pb solder, or other Pb-based plumbing materials that may contaminate drinking water during its delivery from its source to homes. Corrosion of these older plumbing materials can result in leaching of Pb into drinking water (CDC 2012b; Hanna-Attisha et al. 2016). Flint, Michigan is an example of how a water system with Pb sources in drinking water infrastructure resulted in elevated Pb levels in drinking water. For decades, the drinking water for the City of Flint was purchased from the Detroit Water and Sewer Department (DWSD). This water had optimized corrosion control and was treated with orthophosphate, a corrosion inhibitor that reduces Pb solubility and leaching from leaded plumbing materials by the formation of protective scales on the pipe's interior surface. When the water source was changed to the Flint River in 2014, corrosion control was not implemented, which allowed Pb to leach into the drinking water (EPA 2017e). Pb concentration in first-draw tap water tends to be higher than after the plumbing system has been flushed, although with Pb service lines, it is possible to see higher Pb concentrations in flushed water, if flushing is sufficient to draw stagnant water from the service line to the tap. Gulson et al. (1997a) measured Pb in household water throughout the day when the plumbing system of an unoccupied test house was not flushed. Water concentration data ranged from $119 \mu\text{g/L}$ for the initial (first-draw) sample to $35\text{--}52 \mu\text{g/L}$ for hourly samples to $1.7 \mu\text{g/L}$ for a fully flushed sample. The 1991 LCR was implemented to protect public health by minimizing Pb and copper levels in drinking water, by primarily reducing water corrosivity (EPA 2010). The rule set a Pb action level of $15 \mu\text{g/L}$ based on 90th percentile levels of tap

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water samples. The LCR established tap sampling monitoring requirements for public water systems. One-liter samples are taken at the tap where water has stood in the pipes for at least 6 hours (first-draw) in homes and buildings that are considered high-risk of Pb and copper contamination, and the number of samples are based on the system size. Pb action level exceedances can trigger a number of steps that a water system can take to reduce Pb exposure. These requirements include implementing a corrosion control treatment program, monitoring and/or treating source water, public education, and Pb service line replacement (EPA 2004). As discussed in Section 5.5.2, EPA has proposed major changes in the LCR as of October 2019.

Other less common sources of Pb exposure also exist. Exposure may also result from engaging in hobbies that use Pb (e.g., leaded solder is used in making stained glass, molten Pb used in casting, leaded glazes and frits are used in making pottery, and Pb compounds as coloring agents in glassblowing) (Grabo 1997). The use of inadequately glazed or heavily worn earthenware vessels for food storage and cooking may result in Pb exposure (CDC 1985; EPA 1986b). Various folk remedies and Ayurvedic medication (CDC 1998, 2004b, 2012c; Garvey et al. 2001; Wu et al. 1996) and some cosmetics (Mielke et al. 1997) may also be sources of Pb exposure. Moonshine consumption was strongly associated with elevated PbBs (Morgan and Parramore 2001). A 2000 study found a median PbB of 11 µg/dL among 35 moonshine consumers versus 2.5 µg/dL in 68 randomly-selected nonmoonshine consumers (Parramore et al. 2001). Exposure to infants and children can occur from mouthing of leaded jewelry and toys containing Pb or painted with leaded paint (CDC 2018c).

Plastic food wrappers may be printed with pigments that contain Pb chromates. Plastic wrappers used for 14 different national brands of bread collected in New Jersey contained a mean concentration of 26 mg of Pb for a bag size of 2,000 cm². A survey of 106 homemakers who buy such breads indicated that 39% of them reused the bags and 16% of the respondents turned the bags inside out to reuse them, suggesting that the potential exists for Pb leaching from the paint into the stored food (Weisel et al. 1991).

Blood Pb levels measured as a part of the NHANES revealed that between 1976 and 1991, the mean PbBs of the U.S. population aged 1–74 years old dropped 78%, from 12.8 to 2.8 µg/dL. The prevalence of PbBs ≥10 µg/dL also decreased sharply from 77.8 to 4.3%. The major cause of the observed decline in PbBs is most likely the removal of 99.8% of Pb from gasoline and the removal of Pb from soldered cans (Pirkle et al. 1994). Data from the Fourth National Report on Human Exposure to Environmental Chemicals are summarized in Tables 5-20 and 5-21, which provide geometric means of Pb levels in the blood and urine in segments of the U.S. population.

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Table 5-20. Geometric Mean Blood Lead Levels ($\mu\text{g}/\text{dL}$) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age for the Years for 2011–2016

	Survey years	Geometric mean (95% confidence interval)	Sample size
Total	11–12	0.973 (0.916–1.04)	7,920
	13–14	0.858 (0.813–0.906)	5,215
	15–16	0.820 (0.772–0.872)	4,988
Age group			
1–5 years	11–12	0.970 (0.877–1.07)	713
	13–14	0.782 (0.705–0.869)	818
	15–16	0.758 (0.675–0.850)	790
6–11 years	11–12	0.681 (0.623–0.744)	1,048
	13–14	0.567 (0.529–0.607)	1,075
	15–16	0.571 (0.523–0.623)	565
12–19 years	11–12	0.554 (0.511–0.601)	1,129
	13–14	0.506 (0.464–0.551)	627
	15–16	0.467 (0.433–0.504)	1,023
20 years and older	11–12	1.09 (1.03–1.16)	5,030
	13–14	0.967 (0.921–1.02)	2,695
	15–16	0.920 (0.862–0.982)	2,610
Gender			
Males	11–12	1.13 (1.06–1.21)	3,968
	13–14	0.994 (0.919–1.08)	2,587
	15–16	1.13 (1.06–1.21)	3,968
Females	11–12	0.842 (0.796–0.890)	3,952
	13–14	0.746 (0.715–0.777)	2,628
	15–16	0.735 (0.679–0.795)	2,500
Race/ethnicity			
Mexican Americans	11–12	0.838 (0.767–0.916)	1,077
	13–14	0.746 (0.685–0.813)	969
	15–16	0.704 (0.659–0.759)	994
Non-Hispanic blacks	11–12	0.998 (0.947–1.05)	2,195
	13–14	0.871 (0.787–0.963)	1,119
	15–16	0.856 (0.763–0.962)	1,070
Non-Hispanic whites	11–12	0.993 (0.914–1.08)	2,493
	13–14	0.882 (0.820–0.950)	1,848
	15–16	0.835 (0.774–0.900)	1,511
All Hispanics	11–12	0.855 (0.793–0.922)	1,931
	13–14	0.742 (0.695–0.793)	1,481
	15–16	0.703 (0.658–0.750)	1,664
Asians	11–12	1.15 (1.06–1.24)	1,005
	13–14	1.01 (0.923–1.11)	510

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Table 5-20. Geometric Mean Blood Lead Levels ($\mu\text{g}/\text{dL}$) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age for the Years for 2011–2016

Survey years	Geometric mean (95% confidence interval)	Sample size
15–16	1.07 (0.976–1.18)	479

Source: CDC 2018a

Table 5-21. Geometric Mean Urine Lead Levels ($\mu\text{g}/\text{dL}$) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age

	Survey years	Geometric mean (95% confidence interval)	Sample size
Total	11–12	0.360 (0.328–0.396)	2,504
	13–14	0.277 (0.257–0.298)	2,664
	15–16		3,061
Age group			
3–5 years	15–16	0.257 (0.225–0.292)	486
6–11 years	11–12	0.346 (0.292–0.410)	399
	13–14	0.222 (0.192–0.258)	402
	15–16	0.346 (0.292–0.410)	399
12–19 years	11–12	0.259 (0.219–0.305)	390
	13–14	0.201 (0.166–0.245)	451
	15–16	0.196 (0.183–0.211)	402
20 years and older	11–12	0.381 (0.348–0.416)	1,715
	13–14	0.297 (0.280–0.315)	1,811
	15–16	0.304 (0.276–0.334)	1,794
Gender			
Males	11–12	0.414 (0.367–0.466)	1,262
	13–14	0.315 (0.295–0.337)	1,318
	15–16	0.313 (0.285–0.343)	1,524
Females	11–12	0.316 (0.282–0.355)	1,242
	13–14	0.245 (0.222–0.269)	1,346
	15–16	0.259 (0.233–0.288)	1,537
Race/ethnicity			
Mexican Americans	11–12	0.372 (0.320–0.431)	317
	13–14	0.277 (0.240–0.319)	453
	15–16	0.259 (0.233–0.288)	585
Non-Hispanic blacks	11–12	0.431 (0.385–0.483)	669
	13–14	0.371 (0.320–0.429)	581
		0.340 (0.298–0.388)	671
Non-Hispanic whites	11–12	0.346 (0.311–0.385)	820
	13–14	0.267 (0.245–0.290)	985
	15–16	0.275 (0.247–0.305)	924
All Hispanics	11–12	0.372 (0.327–0.423)	573

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Table 5-21. Geometric Mean Urine Lead Levels ($\mu\text{g}/\text{dL}$) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age

	Survey years	Geometric mean (95% confidence interval)	Sample size
Asians	13–14	0.270 (0.239–0.305)	701
	15–16	0.284 (0.258–0.312)	982
	11–12	0.383 (0.341–0.429)	353
	13–14	0.257 (0.230–0.287)	292
	15–16	0.292 (0.264–0.324)	332

Source: CDC 2019

The Adult Blood Lead Epidemiology and Surveillance (ABLES) program tracks adult (aged ≥ 16 years) cases with elevated PbBs from workplace exposure. In 2016, 26 states submitted PbB data on 18,093 adults with PbBs $\geq 10 \mu\text{g}/\text{dL}$. PbBs $\geq 10 \mu\text{g}/\text{dL}$ declined from 26.6 adults per 100,000 employed in 2010 to 15.8 per 100,000 employed in 2016 (results for data submitted as of December 2018). In 2016, among adults with known exposures, 90.3% had occupational exposure. The majority of these adults were employed in manufacturing, construction, mining, and services. Table 5-22 presents industries within each sector with the most workers with occupational exposures resulting in PbB $\geq 25 \mu\text{g}/\text{dL}$ during 2010–2016 (NIOSH 2017a).

Table 5-22. Industries by Sector with Most Workers having Blood Lead Concentrations (PbBs) $\geq 25 \mu\text{g}/\text{dL}$, 2010–2016

NORA Sector	Industry NAICS Code
Manufacturing	Storage battery manufacturing (33591)
	Nonferrous metal (except copper and aluminum) rolling, drawing, extruding, and alloying (33149)
	Alumina and aluminum production and processing (33131)
	Nonferrous metal foundries (33152)
	Nonferrous metal (except aluminum) smelting and refining (33141)
	Other basic inorganic chemical manufacturing (32518)
	Motor vehicle electrical and electronic equipment manufacturing (33632)
Construction	Painting and wall covering contractors (23832)
	Highway, street, and bridge construction (23731)
	Residential building construction (23611)
	Plumbing, heating, and air-conditioning contractors (23822)
	Site preparation contractors (23891)
Services (except public safety)	Commercial and institutional building construction (23622)
	All other amusement and recreation industries (71399)
	Remediation services (56291)

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Table 5-22. Industries by Sector with Most Workers having Blood Lead Concentrations (PbBs) ≥ 25 $\mu\text{g}/\text{dL}$, 2010–2016

NORA Sector	Industry NAICS Code
	Automotive mechanical and electrical repair and maintenance (81111)
	Other services (except public safety industries) (71394)
Mining	Copper, nickel, lead, and zinc mining (21223)

NAICS = North American Industry Classification System; NORA = National Occupational Research Agenda

Source: NIOSH 2017a

Raymond and Brown (2015a, 2015b, 2017) and analyzed the 2007–2012 and 2009–2014 datasets from the Childhood Blood Lead Surveillance (CBLS) system. In 2007, a total of 38 states identified and reported 37,289 children (<6 years) with $\text{PbB} \geq 10$ $\mu\text{g}/\text{dL}$. In 2012, a total of 30 jurisdictions identified and reported approximately 138,000 children (<6 years) with $\text{PbB} \geq 5$ $\mu\text{g}/\text{dL}$. In 2012, federal funding ended and several states lost their state-wide Pb poisoning prevention programs and in 2013, the number of states reporting data declined, as did the number of children reported to the CDC with $\text{PbB} \geq 5$ $\mu\text{g}/\text{dL}$. In October 2013, federal funding resumed and in 2013, 27 states, the District of Columbia, and New York City reported data. In 2014, 30 states, the District of Columbia, and New York City reported data. Table 5-23 summarizes the number and rate per 100,000 children aged <5 years with blood Pb levels 5–9 $\mu\text{g}/\text{dL}$ reported in the 2010–2014 CBLS system. $\text{PbBs} \geq 10$ $\mu\text{g}/\text{dL}$ continue to be more prevalent among children with known risk factors, such as minority race or ethnicity, urban residence, residing in homes built prior to the 1950s, and low family income (CDC 2009).

Table 5-23. Number and Rate per 100,000 Children Aged <5 Years with Blood Lead Levels 5–9 $\mu\text{g}/\text{dL}$ in the Childhood Blood Lead Surveillance System, United States, 2010–2014

Year	<1 Year		1–4 Years	
	Number	Rate	Number	Rate
2010 ^a	18,598	448.48	137,887	805.62
2011 ^b	13,981	352.69	130,838	810.56
2012 ^c	7,876	199.74	95,854	596.58
2013 ^d	5,494	138.26	57,293	360.46
2014 ^e	5,904	148.51	70,680	444.49

^a37 jurisdictions reporting.^b36 jurisdictions reporting.^c30 jurisdictions reporting.^d29 jurisdictions reporting.^e32 jurisdictions reporting.

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Table 5-23. Number and Rate per 100,000 Children Aged <5 Years with Blood Lead Levels 5–9 µg/dL in the Childhood Blood Lead Surveillance System, United States, 2010–2014

Year	<1 Year		1–4 Years	
	Number	Rate	Number	Rate

Source: Raymond and Brown 2017

Various studies suggest that ingestion of game hunted with Pb shot is associated with increased PbBs. Johansen et al. (2006) collected blood samples from 50 men in Nuuk, Greenland to study the relationship between the consumption of birds hunted with Pb shot and PbBs. Men who regularly ate hunted birds killed with Pb shot had mean PbB ranging from 6.2 µg/dL in the group eating 0.1–5 bird equivalents per month to 12.8 µg/dL in those eating >30 bird equivalents per month. In addition, levels were highest in mid-winter when consumption of hunted birds was highest. Those who did not consume hunted birds had a mean PbB of 1.5 µg/dL. These results are consistent with earlier surveys of Arctic hunting communities. A 1992 survey of 492 Inuit adults from the Arctic region of Quebec, Canada showed that consumption of waterfowl, along with age and smoking, were associated with elevated PbB (Dewailly et al. 2001). The geometric mean PbB was 0.42 µmol/L (8.7 µg/dL), with a range of 0.04–2.28 µmol/L (0.8–47 µg/dL). In a cohort of Inuit newborns from northern Quebec, where the population consumed game killed with Pb shot, the geometric umbilical cord PbB was 3.9 µg/dL (range 0.2–27 µg/dL); 7% of Inuit newborns had cord PbBs >10 µg/dL as compared to 0.16% of the non-Inuit population in southern Quebec (Lévesque et al. 2003).

Second-hand smoke may also contribute to increased Pb exposure (Apostolou et al. 2012; Mannino et al. 2003; Richter et al. 2013). Pb is a component of tobacco and tobacco smoke, and smokers often have higher Pb blood levels than nonsmokers (Bonanno et al. 2001; Mannino et al. 2003). Using data from the NHEXAS EPA Region V study, PbB levels in smokers and nonsmokers were analyzed and a correlation between tobacco smoke and exposure levels was observed (Bonanno et al. 2001). The mean PbBs in smokers, nonsmokers exposed to environmental tobacco smoke (ETS), and nonsmokers without ETS were 2.85, 2.06, and 1.81 µg/dL, respectively (Bonanno et al. 2001). Recent Pb urine concentrations for the U.S. adult population from the NHANES by smoking status are presented in Table 5-24.

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Table 5-24. Geometric Mean Urine Lead Levels ($\mu\text{g/dL}$) and the 95th Percentile Confidence Interval by Smoking Status

	Survey years	Geometric mean (95% confidence interval)	Sample size
Cigarette smokers			
Total	11–12	2.36 (1.71–4.62)	876
	13–14	1.51 (1.30–1.91)	957
Age group			
20–49 years	11–12	1.78 (1.41–3.07)	522
18–49 years	13–14	1.34 (1.13–1.92)	583
50 years and older	11–12	3.35 (1.62–6.83)	354
	13–14	1.72 (1.40–2.03)	374
Gender			
Males	11–12	3.07 (1.73–5.03)	527
	13–14	1.91 (1.48–2.14)	512
Females	11–12	1.58 (1.14–3.45)	349
	13–14	1.30 (1.12–1.41)	445
Nonsmokers^a			
Total	11–12	1.38 (1.25–1.58)	1,343
	13–14	1.16 (0.950–1.51)	1,487
Age group			
20–49 years	11–12	1.26 (1.02–1.38)	671
18–49 years	13–14	0.880 (0.720–1.04)	778
50 years and older	11–12	1.63 (1.29–2.16)	672
	13–14	1.48 (1.12–2.52)	709
Gender			
Males	11–12	1.61 (1.18–2.13)	635
	13–14	1.51 (1.04–2.68)	663
Females	11–12	1.32 (1.06–1.38)	708
	13–14	0.238 (0.219–0.258)	824

^aCigarette nonsmokers who used other tobacco products were excluded.

Source: CDC 2018a

Studies have been conducted to determine exposure of firearm instructors to Pb at outdoor firing ranges when either nonjacketed (pure Pb) or jacketed (copper-coated) bullets were used. Instructors are likely to have higher exposure than shooters because they spend more time at the range. In studies at an outdoor range in Virginia, the mean breathing zone Pb level when nonjacketed bullets were fired was $67.1 \mu\text{g}/\text{m}^3$ for one instructor and $211.1 \mu\text{g}/\text{m}^3$ for another (Tripathi and Llewellyn 1990). When jacketed bullets were used, breathing zone levels decreased to $\leq 8.7 \mu\text{g}/\text{m}^3$. PbBs of the instructors did not exceed the OSHA Pb standard's medical removal level of $2.4 \mu\text{mol/L}$ ($60 \mu\text{g/dL}$) in either case (OSHA 2016a).

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When shooters fired conventional Pb bullets, their mean exposures to airborne Pb were $128 \mu\text{g}/\text{m}^3$ in the personal breathing zone and $68 \mu\text{g}/\text{m}^3$ in the general area. When totally copper-jacketed Pb bullets were fired, the mean breathing zone and general area air sample concentrations were 9.53 and $5.80 \mu\text{g}/\text{m}^3$, respectively (Tripathi and Llewellyn 1990). At an outdoor uncovered range in Los Angeles, instructors who spent an average of 15–20 hours/week behind the firing line were found to be exposed to breathing zone Pb concentrations of 460 and $510 \mu\text{g}/\text{m}^3$ measured as 3-hour, time-weighted averages. The PbB of one instructor reached $3.38 \mu\text{mol}/\text{L}$ ($70 \mu\text{g}/\text{dL}$). After reassignment to other duties, repeat testing indicated his PbB had dropped to $1.35 \mu\text{mol}/\text{L}$ ($28 \mu\text{g}/\text{dL}$) (Goldberg et al. 1991).

In 1991, NIOSH conducted a survey of the Federal Bureau of Investigations (FBI) Firearms Training Unit firing ranges and related facilities to determine occupational Pb exposures among FBI and Drug Enforcement Agency (DEA) firing range personnel (NIOSH 1996b). Sixty-one personal breathing-zone and 30 area samples for airborne Pb were collected. Exposures ranged up to $51.7 \mu\text{g}/\text{m}^3$ (mean, $12.4 \mu\text{g}/\text{m}^3$), $2.7 \mu\text{g}/\text{m}^3$ (mean, $0.6 \mu\text{g}/\text{m}^3$), and $4.5 \mu\text{g}/\text{m}^3$ (mean, $0.6 \mu\text{g}/\text{m}^3$) for range instructors, technicians, and gunsmiths, respectively. Exposure of custodians ranged from nondetectable to $220 \mu\text{g}/\text{m}^3$ during short-term cleaning of a large indoor range. Carpet dust sampling of dormitory rooms of students who practiced at the firing ranges revealed higher ($p < 0.0005$) dust-Pb concentrations when compared to nonstudent dormitories (dust-Pb concentration range of 116 – $546 \mu\text{g}/\text{g}$ with a geometric mean of $214 \mu\text{g}/\text{g}$ in the student's rooms versus a dust-Pb concentration range of 50 – $188 \mu\text{g}/\text{g}$ with a geometric mean of $65 \mu\text{g}/\text{g}$ for the nonstudent rooms). This suggested that the students were contaminating their living quarters with Pb.

The American Academy of Pediatrics (AAP) (1998, 2005) concluded that although monitoring data demonstrate a decline in PbBs, Pb remains a common, preventable, environmental health threat. Most Pb poisoning in children is the result of dust and chips from deteriorating Pb paint on interior surfaces (AAP 2005, 2016; ATSDR 2017). The AAP supported the CDC guidelines endorsing universal screening in certain areas and targeted screening for children at high risk (CDC 1997b, 2005). Many children continue to be at risk for ingestion of Pb-based paint and of soil and dust contaminated through the deterioration of Pb-based paint and the residues from combustion of leaded gasoline. A 1974 study indicated that elevated PbBs in children were most likely a result of ingesting Pb-contaminated soil, and that the most likely source was Pb-based paint rather than Pb from automotive exhaust (Ter Haar and Aronow 1974). However, more recent studies have shown that children with the highest PbBs live in areas with high traffic flow where Pb particles in the air may fall directly to the soil or adhere to the outer surfaces of building and wash to the soil with rain (Mielke et al. 1989, 2008, 2010). The CDC concluded that a

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common source of Pb exposure for children who have elevated PbB is Pb-based paint that has deteriorated into paint chips and Pb dusts (CDC 1997b, 2012d).

Pb can readily cross the placenta; therefore, exposure of women to Pb during pregnancy results in uptake by the fetus. Furthermore, since the physiological stress of pregnancy may result in mobilization of Pb from maternal bone, fetal uptake of Pb can occur from a mother who was exposed to Pb before pregnancy, even if no Pb exposure occurs during pregnancy. Maternal Pb can also be transferred to breastfeeding infants.

Malcoe et al. (2002) assessed Pb sources and their effect on blood Pb in rural Native American and white children living in a former mining region. Blood samples, residential environmental samples (soil, dust, paint, water), and caregiver interviews (hand-mouth behaviors, socioeconomic conditions) were obtained from a representative sample of 245 children ages 1–6 years. There were no ethnic differences in the results. However, poor children were especially vulnerable. Regression analysis showed that mean floor dust Pb loading $>10.1 \mu\text{g}/\text{ft}^2$ and yard soil Pb $>165.3 \text{ mg}/\text{kg}$ were independently associated with blood Pb levels $\geq 10 \mu\text{g}/\text{dL}$.

The Pb content of dusts can be a significant source of exposure, especially for young children. Baseline estimates of potential human exposure to dusts, including intake due to normal hand-to-mouth activity, are 0.2 g/day for children 1–6 years old versus 0.1 g/day for adults when both indoor and outdoor ingestion of soil including dust is considered (EPA 1989a). For children who engage in pica behavior (the compulsive, habitual consumption of nonfood items), the ingestion rate of soil can be as high as 5 g/day. Although ingestion of Pb-containing paint may lead to elevated PbBs in young children, a major source of elevated PbBs ($>10 \mu\text{g}/\text{dL}$) in children is often contaminated household dust and subsequent hand contamination and repetitive mouthing (Bornschein et al. 1986; Charney et al. 1980; Dixon et al. 2009; Lanphear and Roghmann 1997; Lanphear et al. 1998a; Succop et al. 1998). Weathering of Pb-based paint can contribute to the Pb content of dust and soil. Pb levels of indoor dust and outdoor soil were found to be strongly predictive of PbBs in over 200 urban and suburban infants followed from birth to 2 years of age; however, PbBs were not correlated with indoor air or tap water Pb levels, nor the size of nearby roadways. Indoor dust Pb levels and soil Pb levels in the homes of children with high PbBs ($>8.8 \mu\text{g}/\text{dL}$) were 72 $\mu\text{g}/\text{wipe}$ (window sill dust) and 1,011 $\mu\text{g}/\text{g}$, respectively; children with low PbBs ($<3.7 \mu\text{g}/\text{dL}$) were exposed to 22 $\mu\text{g}/\text{wipe}$ and 380 $\mu\text{g}/\text{g}$, respectively. In addition, 79% of the homes of children with high PbBs had been renovated, while only 56% of the homes of children with low PbBs had been renovated, suggesting that renovating the interior of homes previously painted with leaded paint may

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increase, at least temporarily, a child's exposure to Pb dust (Rabinowitz et al. 1985). Regular use of dust control methods (e.g., wet mopping of floors, damp-sponging of horizontal surfaces, high-efficiency vacuum cleaner) has been shown in some, although not all, cases to reduce indoor dust, Pb dust, and blood Pb levels in some, although not all, older homes containing leaded paints (Lanphear et al. 2000b; Rhoads et al. 1999). Decreases of between 17 and 43% in blood Pb concentrations were observed in children where regular dust control methods had been used to reduce indoor levels of Pb (Rhoads et al. 1999). EPA (2014c) summarized concentrations of Pb in house dust in the United States from 2006 to 2011; these data are presented in Table 5-25.

PbB samples from 1,473 children <5 years old were analyzed prior to and after the change in drinking water source in the city of Flint, Michigan (Hanna-Attisha et al. 2016). Prior to the change, 2.4% of the children had PbB levels exceeding 5 µg/dL (n=736). Following the change in water source, 4.9% of children's PbB levels exceeded 5 µg/dL for samples obtained from January 1 to September 15, 2015 (n=737). The study also found that in areas where ≥25% of the drinking water samples exceeded 15 µg/L, the percentage of children with PbB levels >5 µg/dL increased from 4.0 to 10.6%. Gomez et al. (2018) analyzed PbB levels for children <5 years old in Flint, Michigan over an 11-year time span from 2006 to 2016. The percentage of children with PbB levels >5.0 µg/dL declined from 11.8% in 2006 to 3.2% by 2016. The study authors noted an uptick in the geometric mean PbB level during the height of the Flint water crisis from 1.19±0.02 to 1.30±0.02 µg/dL in 2014–2015, but it declined to 1.15±0.02 µg/dL in 2016 after the water source was switched back to the DWSD. The authors concluded that while there was a slight increase in PbB levels during the time at which the source of drinking water was changed for residents of Flint, the overall trend for the 11-year time span was decreasing PbB levels with a nearly 73% reduction in the percentage of children having levels >5 µg/dL. A second study analyzed PbB levels for females aged 12–50 years prior to (April 25, 2012–October 15, 2013), during (April 25, 2014–October 15, 2015), and immediately after (April 25, 2016–October 15, 2017) the Flint water crisis (Gomez et al. 2019). The authors found that blood levels did not increase for females of child-bearing age residing in Flint during the period when the water supply was changed from the DWSD to the Flint River. The geometric means reported were 0.69 µg/dL (April 25, 2012–October 15, 2013), 0.65 µg/dL (April 25, 2014–October 15, 2015), and 0.55 µg/dL, (April 25, 2016–October 15, 2017).

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Table 5-25. Measurements of Lead in Indoor Dust in the United States from 2006 to 2011

Location	Sample site	Value reported
New York City, New York	Glass plate next to open window of academic building	Median weekly dust loading: 52 µg/m ²
Eureka, Utah near Eureka Mills Superfund Site	Indoor home site (not specified)	Dust concentrations, range: 160–2,000 mg/kg
Denver, Colorado, near Vasquez Blvd and I-70 Superfund Site	Indoor home site (not specified)	Dust concentrations, range: 11–660 mg/kg
East Helena, Montana, near East Helena Superfund Site	Indoor home site (not specified)	Dust concentrations, range: 68–1,000 mg/kg
Syracuse, New York	Floor	Dust concentrations, range: 209–1,770 mg/kg
United States (nationwide)	Smooth floor	Median dust loading: 1.7 µg/m ² Average dust loading: 4.4 µg/m ²
	Rough floor	Median dust loading: 5.6 µg/m ² Average dust loading: 16 µg/m ²
	Smooth windowsill	Median dust loading: 2.5 µg/m ² Average dust loading: 190 µg/m ²
	Rough windowsill	Median dust loading: 55 µg/m ² Average dust loading: 480 µg/m ²
Milwaukee, Wisconsin	Central perimeter	Average dust concentration: 107 µg/m ²
	Entry	Average dust concentration: 140 µg/m ²
	Window	Average dust concentration: 151 µg/m ²
Rural towns, Idaho	Vacuum	Dust concentration Median: 120 mg/kg Maximum: 830 mg/kg
	Floor	Median dust concentration: 95 mg/kg Maximum dust concentration: 1,300 mg/kg
Bunker Hill, Idaho Superfund Site	Vacuum	Median dust concentration: 470 mg/kg Maximum dust concentration: 2,000 mg/kg
	Floor	Median dust concentration: 290 mg/kg Maximum dust concentration: 4,600 mg/kg

Source: EPA 2014c

Lanphear and Roghmann (1997) and Lanphear et al. (1996a, 1996b, 1998b) studied factors affecting PbBs in urban children and found the following independent predictors of children's PbBs: dust Pb loading in homes (carpets, uncarpeted floors, window sills, and troughs), African-American race/ethnicity, foundation perimeter soil Pb levels, ingestion of soil or dirt, Pb content and condition of interior painted surfaces, and first-flush kitchen drinking water Pb levels (Lanphear et al. 1996a, 1996b). Differences in housing conditions and exposures to Pb-containing house dust appear to contribute to the

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racial differences in urban children's PbBs. In addition, white children were more likely to put soil in their mouths (outdoor exposure) and suck their fingers, and African-American children were more likely to put their mouths on window sills (indoor exposure) and to use a bottle. Interior Pb exposures were more significant for African American children and exterior Pb exposures were more significant for white children (Lanphear et al. 1996a, 1996b). Mouthing behaviors are an important mechanism of Pb exposure among urban children (Lanphear and Roghmann 1997). Community characteristics such as residence within a city, proportion of African Americans, lower housing value, housing built before 1950, higher population density, higher rates of poverty, lower percent of high school graduates, and lower rates of owner-occupied housing have been used to identify children with elevated blood levels (Lanphear et al. 1998b). An analysis of children's PbBs and multiple measures of Pb concentrations in household dust, tap water, foundation perimeter soil, and interior house paint has been used to predict the effect of changing concentrations of Pb in environmental media on children's PbBs. An increase in dust Pb loading from background to 200 $\mu\text{g}/\text{ft}^2$ was estimated to produce an increase of 23.3% in the percentage of children estimated to have a PbB $>10 \mu\text{g}/\text{dL}$; an increase in tap water Pb concentration from background to 15 $\mu\text{g}/\text{L}$ was estimated to produce an increase of 13.7% in the percentage of children estimated to have a PbB level $>10 \mu\text{g}/\text{dL}$; and an increase in soil Pb concentration from background to 400 $\mu\text{g}/\text{g}$ was estimated to produce an increase of 11.6% in the percentage of children estimated to have a PbB level $>10 \mu\text{g}/\text{dL}$ (Lanphear et al. 1998a).

Outdoor Pb dust was found to be a more potent contaminant of children's hands than indoor dust at daycare centers in New Orleans; boys, in general, had higher hand Pb levels than girls. The conclusions were based on Pb analysis of hand wipe samples taken before and after children played outdoors at four different daycare centers (a private inner-city site, a private outer-city site, a public inner-city site, and a public outer-city site). The private inner-city site had a severely contaminated outdoor play area with measured soil Pb concentrations ranging from 287 to 1,878 mg/kg . The outdoor play area at the public inner-city site, where children exhibited the lowest hand Pb measurements of any site in the study, had been completely paved over with concrete or rubberized asphalt and had well-maintained equipment (Viverette et al. 1996).

EPA conducted the Urban Soil Lead Abatement Demonstration Project (USLADP), also known as the "Three City Lead Study," in Boston, Baltimore, and Cincinnati (EPA 1996c). The purpose was to determine whether abatement of Pb in soil could reduce PbBs of inner-city children. No significant evidence was found that soil abatement had any direct impact on children's PbBs in either the Baltimore or Cincinnati studies. In the Boston study, however, a mean soil Pb reduction of 1,856 ppm resulted in a

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mean decline of 1.28 µg/dL PbB at 11 months postabatement (Weitzman et al. 1993). Phase II extended the study to 2 years and included soil abatement of the two comparison areas from Phase I (Aschengrau et al. 1994). Combined results from Phase I and II suggested a higher impact of soil remediation on PbBs (2.2–2.7 µg/dL). EPA reanalyzed the data from the USLADP in an integrated report (EPA 1996c). They concluded that when soil is a significant source of Pb in the child's environment, under certain conditions, the abatement of that soil will result in a reduction in exposure and consequently, PbB level. The results of the USLADP suggest that a number of factors are important in determining the influence of soil remediation on PbBs in children. These include the site-specific exposure scenario, the magnitude of the remediation, and the magnitude of additional sources of Pb exposure.

Authors of a study of PbBs in children in Toronto, Canada, before and after abatement of Pb-contaminated soil and house dust found that they could neither strongly support nor refute beneficial effects of abatement. The failure to reach a definite conclusion from the results of the study, which included data from 12 cross-sectional blood-screening surveys that were conducted over an 8-year period, was due, in part, to a low response rate (32–75%) to questionnaires used to determine behavioral, household, lifestyle, neighborhood, and environmental factors relating to study participants (Langlois et al. 1996).

Seasonal variations in PbBs in children have been observed in a number of studies (Gulson et al. 2008; Haley and Talbot 2004; Havlena et al. 2009; Kemp et al. 2007; Johnson and Bretsch 2002; Johnson et al. 1996; Laidlaw et al. 2005; Yiin et al. 2000). These studies suggest a general trend of increasing PbB during late summer and early fall. In addition to seasonal patterns in behavior (e.g., outdoor activities), seasonal patterns in weather (humidity and wind velocity) that promote re-entrainment and transport of dust Pb may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012).

In addition to the ingestion of hand soil/dust through normal hand-to-mouth activity, some children engage in pica behavior (consumption of nonfood items), which can put them at increased risk through ingestion of large amounts of soil contaminated with Pb. It has been estimated that an average child may ingest between 20 and 50 mg of soil/day and that a pica child may ingest ≥5,000 mg of soil/day (LaGoy 1987; Mielke et al. 1989). If the soil contains 100 µg/g of Pb, an average child may be exposed to 5 µg Pb/day from this source alone (Mielke et al. 1989), and a pica child may be exposed to >100 times that amount.

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Improper removal of Pb from housing known to contain Pb-based paint can significantly increase Pb levels in dust, thus causing Pb toxicity in children living in the home during the Pb-removal process. Four such cases have been documented (Amitai et al. 1987). In January 1995, the New York State Department of Health identified 320 children in 258 households in New York State (excluding New York City) with PbBs ≥ 20 $\mu\text{g/dL}$ that were considered to be attributable to residential renovation and remodeling (CDC 1997a).

Workers occupationally exposed to Pb can carry Pb home on clothing, bodies, or tools (take home exposure). PbBs of children in households of occupationally exposed workers were almost twice those of children in neighboring homes whose parents were not occupationally exposed to Pb (median ranges were 10–14 and 5–8 $\mu\text{g/dL}$, respectively) (Grandjean and Bach 1986). Young children (<6 years old) of workers exposed to high levels of Pb in workplace air at an electronic components plant (61–1,700 $\mu\text{g Pb/m}^3$ ambient concentrations) had significantly elevated PbBs (13.4 $\mu\text{g/dL}$) compared with children from the same locale whose parents did not work in the electronics plant (7.1 $\mu\text{g/dL}$) (Kaye et al. 1987). Based upon data collected from 1987 to 1994, children aged 1–5 years ($n=139$) of workers whose occupation resulted in Pb exposure had a geometric mean PbB of 9.3 $\mu\text{g/dL}$ as compared to a U.S. population geometric mean of 3.6 $\mu\text{g/dL}$ (Roscoe et al. 1999). Of this group, 52% of the children had PbBs ≥ 10 $\mu\text{g/dL}$ compared to 8.9% of the U.S. population and 21% had PbBs ≥ 20 $\mu\text{g/dL}$ compared to 1.1% of the U.S. population (Roscoe et al. 1999). However, improved industrial hygiene procedures are likely to have decreased worker take-home exposures. Exposures of Pb workers' families have been identified in nearly 30 different industries and occupations. Industries in which exposure of family members has been reported most often include Pb smelting, battery manufacturing and recycling, radiator repair, electrical components manufacturing, pottery and ceramics, and stained glass making (NIOSH 1995). Children of Pb-exposed construction workers may also be at increased risk (Whelan et al. 1997).

Children may be exposed to Pb because of activities associated with certain hobbies and artistic activities practiced by adults in the home. Some of the more obvious hobbies and activities involving use of Pb-containing materials include casting, stained glass, pottery, painting, glassblowing, and screenprinting. Activities involving use of Pb-containing materials should always be done in an area well-ventilated with outdoor air and should never be done with children in the same room or in close proximity. Maas et al. (2005) indicated that high levels of Pb are prevalent in inexpensive cosmetic jewelry that is sold to the general public at retail stores.

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Accidental or intentional ingestion of folk remedies (e.g., Chinese herbal medicines and Ayurvedic medicines containing Pb) or use of the Pb containing eye cosmetic tiro in children (discussed in Section 5.5.5) represents another source for potential Pb-poisoning in children. Sindoor, a cosmetic and cultural/religious powder used in Hindu cultures, has been found to contain very high amounts of Pb (Lin et al. 2010). Hair dyes formulated with Pb acetate represent a potential source for Pb-poisoning both by accidental ingestion and by hand-to-mouth activity following contact with Pb-contaminated surfaces, including dyed hair of adults (Mielke et al. 1997).

Children may be exposed to Pb through the inhalation of second-hand smoke. Mannino et al. (2003) employed data from the NHANES III and analyzed PbBs of children aged 4–16 years who were exposed to high, low, and intermediate levels of second-hand smoke. Serum levels of the nicotine biomarker cotinine were used to classify the children into one of the three second-hand smoke exposure categories. The geometric mean PbBs were 1.5, 1.9, and 2.6 µg/dL for children with low (≤ 0.050 –0.104 ng/mL), intermediate (0.105–0.562 ng/mL), and high (0.563–14.9 ng/mL) serum cotinine levels, respectively (Mannino et al. 2003).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers exposed to Pb in the workplace and family members of workers exposed via take home exposure, other population groups are at risk for potential exposure to high levels of Pb. These include populations residing in older housing or buildings that contain deteriorating leaded paint or that have galvanized pipes, Pb service lines, or scales that contain Pb within a distribution public water system; in high-traffic areas with legacies from leaded gasoline; near sites where Pb was produced or disposed; or near one of the NPL hazardous waste sites where Pb has been detected in some environmental media (ATSDR 2017b; EPA 2014c, 2016a). Since Pb is often detected in tobacco and tobacco smoke, persons who use chewing tobacco or smoke or are exposed to second-hand smoke, may have higher PbB levels than persons that do not use these products (Apostolou et al. 2012; Bonanno et al. 2001; Richter et al. 2013). Recent studies have also found e-cigarettes to be a potential source of Pb exposure (Olmedo et al. 2018). Other Pb sources that can contribute to elevated exposures to individual children or adults include mouthing or ingestion of toys containing Pb and consumption of candy and folk remedies and illicitly manufactured drugs that contain Pb (CDC 2002b, 2018c).

General population exposure is most likely to occur through the ingestion of food and water contaminated with Pb. Based on a multimedia Pb exposure modeling analysis for children 1–5 years old at upper

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percentiles of PbB in the U.S. population, soil and dust ingestion are dominant exposure pathways, but for lower percentiles, other age groups (e.g., younger children), or specific local U.S. locations, the main exposure source/pathway could be different (Zartarian et al. 2017). However, some individuals and families may be exposed to additional sources of Pb in their homes. This is particularly true of older homes that may contain Pb-based paint. In an attempt to reduce the amount of exposure due to deteriorating leaded paint, the paint is commonly removed from homes by burning (gas torch or hot air gun), scraping, or sanding. These activities have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. In addition, those individuals involved in the paint removal process (i.e., do-it-yourself renovators and professionals who remove Pb) can be exposed to such excessive levels that Pb poisoning may occur (Chisolm 1986; Fischbein et al. 1981; Rabinowitz et al. 1985). Special populations at risk of high exposure to tetraethyl Pb include workers at hazardous waste sites and those involved in the manufacture and dispensing of tetraethyl Pb (Bress and Bidanset 1991).

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of Pb is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of Pb.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of exposure of humans Pb that are discussed in Chapter 2 are summarized in Figure 2-1. The purpose of this figure is to illustrate the information concerning the health effects of Pb. The number of human studies included in the profile for each endpoint is indicated regardless of whether an effect was found.

The health effects of Pb have been extensively studied in humans, including numerous studies in children. Due to the extent of the database in humans, a comprehensive review of the complete epidemiological database is not feasible. Epidemiological studies included in Chapter 2 were selected to identify the major lines of evidence regarding health effects in humans. Because the database of epidemiological studies is so large, animal studies were not included in the profile. Due to the increasing awareness that low-level environmental exposure resulting in blood Pb concentrations (PbB) $<10 \mu\text{g/dL}$ is associated with adverse effects, particularly in children, the primary objective of current research is focused on health effects associated with $\text{PbB} \leq 10 \mu\text{g/dL}$. Additional details on studies with $\text{PbB} \leq 10 \mu\text{g/dL}$, including statistical analyses and assessment of confounding factors, are provided in the *Supporting Document for Epidemiological Studies for Lead*.

Health effects of Pb in humans are not defined in terms of route or duration of exposure. Epidemiological studies on Pb toxicity rely on internal exposure metrics (e.g., PbB), rather than measurements of external

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exposures (e.g., concentration of Pb in water or air) or ingested dose. Furthermore, once absorbed into the body, the health effects of Pb are the same, regardless of the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb can be retained in the body for decades; therefore, health effects of Pb in humans are considered to be associated with chronic exposure, rather than to shorter exposures.

6.2 IDENTIFICATION OF DATA NEEDS

A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Increased awareness of the potential adverse consequences of low environmental exposures to Pb has led to changes in U.S. public health policy, with a focus on lowering PbB levels to well below 10 µg/dL (CDC 2012d; EPA 2016b). In 2012, the CDC concluded that the 97.5th percentile of the U.S. PbB distribution (based on NHANES data) should be considered a reference value for identifying children who have "elevated" PbB (CDC 2012d). At that time, the 97.5th percentile was approximately 5 µg/dL. Therefore, additional epidemiological studies for all health outcomes are needed. The objective of these additional studies would be to define the low end of the dose-response curve (e.g., at PbB ≤ 5 µg/dL) and to identify threshold levels for health outcomes.

MRLs. Epidemiological studies have identified health effects of Pb in all organ systems. However, exposure thresholds for effects have not been identified, and it is not possible to determine from the epidemiological data which organ system are the most sensitive (i.e., primary) targets for Pb toxicity. Because clear thresholds for these effects have not been identified, MRLs for Pb have not been derived. Additional epidemiological studies would provide more data to further characterize effects; however, as PbBs continue to decline and effects are observed at the lowest PbB examined, identification of control groups has become increasingly difficult. Thus, it is not anticipated that additional epidemiological studies would identify threshold values for Pb-induced toxicity endpoints.

Health Effects. As noted above, epidemiological studies have identified health effects of Pb in every organ system at the lowest PbB evaluated. Additional prospective studies on all health outcomes would provide important information to further characterize the effects of Pb and evaluate potential implications

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for long-term effects. However, as noted above, it is not anticipated that additional epidemiological studies would identify threshold values for health effects.

Epidemiology and Human Dosimetry Studies. Several models of the Pb exposure-biokinetics toxicokinetics in humans have been developed and used in dosimetry studies. Additional studies would be helpful for addressing major uncertainties in these models, including: (1) absence of calibration data for the kinetics of Pb in blood and bone in children in association with exposures that have been quantified with high certainty; (2) absence of calibration data on bone Pb concentrations in adolescents and adults in association with exposures that have been quantified with high certainty; (3) absence of data on the absolute bioavailability of ingested Pb in older children and adolescents; (4) incomplete understanding of Pb kinetics during periods of changing bone metabolism, including adolescence, pregnancy, and menopause; and (5) incomplete understanding of inter- and intra-individual variability in model parameter values in humans. In addition, there is a need for studies that can evaluate or validate model predictions of concentrations of Pb in blood and other tissues in populations in which PbBs are typical of the U.S. population ($\leq 5 \mu\text{g/dL}$).

Biomarkers of Exposure and Effect. Measurement of blood Pb concentration is the most widely used biomarker of Pb exposure and is used to identify children who have elevated exposures. Measurement of bone Pb by XRF has been used to estimate Pb body burden in adults, which is a more accurate biomarker of long-term exposure than PbB. Additional studies that could improve and evaluate the validity of non-invasive biomarkers (e.g., hair, saliva, sweat, deciduous teeth, urine) for quantifying exposure would be helpful for population monitoring of Pb exposures and for epidemiology of Pb health effects.

Absorption, Distribution, Metabolism, and Excretion. Studies of Pb absorption are limited to studies in infants and adults. No data are available on the absorption of Pb in older children and adolescents. Additional studies of Pb absorption in this age category would be useful for improving exposure-biokinetic models.

A variety of factors are known to influence the absorption of ingested Pb, including the chemical form of the ingested Pb, the presence of food in the gastrointestinal tract, diet, and nutritional status with respect to calcium, vitamin D, and iron; however, for the most part, the mechanisms by which these interactions occur are not fully understood. This reflects, in part, a lack of understanding of the mechanisms by which Pb is absorbed in the gastrointestinal tract, and studies aimed at elucidating such mechanisms would be

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helpful for developing PBPK models that accurately simulate relationships between Pb exposure and Pb in blood and other target and biomarker tissue.

The quantitative significance of the dermal absorption pathway as a contributor to Pb body burden remains an uncertainty. Few studies are available on Pb absorption after dermal exposure of inorganic Pb compounds in humans. Children may experience extensive dermal contact with Pb in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic Pb compounds from both aqueous media and from soil would be helpful for improving PBPK models, in particular, studies that enable measurements to be extrapolated to children.

Comparative Toxicokinetics. Animal models (e.g., swine, mouse) have been used extensively as a model for assessing relative bioavailability of Pb in ingested soil in humans and for evaluating *in vitro* approaches to assessing bioaccessibility of Pb. However, no studies are available in which the absolute or relative bioavailability of ingested Pb has been quantitatively compared in animal models and humans. Such studies would be useful for validating both the *in vivo* swine model and the *in vitro* bioaccessibility model.

Children's Susceptibility. Children are likely to have increased susceptibility to Pb compared to adults for several reasons: increased susceptibility of developing physiological systems compared to mature systems; increased absorption of Pb in children compared to adults; and common childhood behaviors (e.g., hand-to-mouth activity, pica behavior [the compulsive, habitual consumption of nonfood items], proximity of breathing zone to entrained surface dust). In addition, several other factors may affect children's susceptibility to Pb, including (but not limited to) family socio-economic status, parent education, parent alcohol, tobacco, and drug use, allergen exposure, and family history of disease, although these factors may not be unique to children. Additional studies evaluating these factors would provide an increased understanding of relative contributions of these factors to child PbB and associated health effects.

Physical and Chemical Properties. No data needs were identified regarding physical and chemical properties of Pb.

Production, Import/Export, Use, Release, and Disposal. Continued monitoring of Pb production, import/export, use, release, and disposal would be helpful for identifying sources of potential human exposure. In particular, additional data on releases of Pb from leaded gasoline used in piston-driven engines would be helpful for determining potential contributions of this source to human exposure. Industrial wastes, as well as consumer products, containing Pb are disposed of in municipal and hazardous waste landfills. Current information on the amounts being disposed would be helpful for evaluating potential for exposures to Pb from these sources.

Environmental Fate. Additional information on the atmospheric transformations of organic and inorganic Pb compounds would be helpful for identifying Pb compounds to which humans are most likely to be exposed by inhalation. Additional data regarding the chemical speciation and the transformation pathways of Pb in soils and water with varying properties such as pH, oxygen content, and salinity would be helpful for improved understanding of the environmental fate of Pb in soils and water.

Bioavailability from Environmental Media. Studies conducted in animal models show that oral RBA of soil Pb varies depending upon the Pb mineralogy and physical characteristics of the Pb in the soil. There is only one published study that assessed the bioavailability of Pb in humans (adults) who ingested hazardous waste site soil. Additional studies of this type would provide an improved basis for estimating Pb uptake in people who are exposed to Pb in soil. No studies have measured oral RBA of surface dusts. Since this is an important exposure pathway, especially in urban environments, studies of oral Pb RBA of surface dusts collected from various types of indoor and outdoor surfaces, including those impacted by paint Pb, would be helpful.

Recent interest in the use of soil-amending agents (e.g., phosphate) to reduce soil Pb bioavailability, would be served by additional studies directed at developing methods for monitoring the magnitude and persistence of the effect of amending agents on Pb bioavailability and for predicting the magnitude of the effect for improved design of amending projects.

Food Chain Bioaccumulation. No data needs were identified regarding food chain bioaccumulation.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of Pb in contaminated media at hazardous waste sites are needed so that the information obtained on levels of Pb in the environment can be used in combination with the known body burden of Pb to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Continued

monitoring of Pb levels in air, drinking water, and diet (e.g., food and bottled water) would be helpful for evaluating potential for exposures to Pb from these sources. Continued testing of consumer products would be helpful for identifying potential localized sources of human exposure (e.g., ceramics, cosmetics, jewelry, toys).

Exposure Levels in Humans. Continued updating of national (e.g., NHANES) and regional surveys of Pb biomarkers (e.g., PbB) would be helpful for assessing temporal and demographic trends in Pb exposure in the U.S. population as well as for evaluating associations between Pb exposure and health metrics (e.g., those included in the NHANES), and for evaluating models that relate exposure to PbB.

Exposures of Children. Since an important variable in estimating Pb intakes from measurements of surface dust Pb levels is the rate of surface dust ingestion, improved estimates of soil ingestion would increase confidence in predictions of Pb intakes associated with exposures to Pb in surface dusts. In some contexts, exposure to surface dust Pb is measured in terms of Pb loading ($\mu\text{g}/\text{Pb}/\text{cm}^2$ of surface area available for contact); however, Pb loading measurements do not provide a direct way of estimating Pb ingestion without corresponding estimates of dust loading and surface dust ingestion rates. Improved methods for translating measurements of Pb loading into estimates of surface dust Pb concentration or surface dust Pb intake would be helpful for improving models for predicting exposure-Pb relationships in children.

6.3 ONGOING STUDIES

Ongoing studies on Pb are outlined in Table 6-1. Note that the studies listed below are funded by the National Institute of Health (NIH) and do not include ongoing studies that are funded by other sources.

Table 6-1. Ongoing Studies on Lead (Pb)			
Investigator	Affiliation	Research description	Sponsor
Bhattacharya, A	University of Cincinnati	Epidemiological study evaluating the effects of childhood Pb exposure on bone and musculature in African-American women	NIEHS
Kordas, K	State University of New York at Buffalo	Epidemiological study on the interaction between metals and neurobehavioral outcomes in children and adolescents	NIEHS
Lamas, G	Mt. Sinai Medical Center	Investigation effects of chelation-reduced PbB on myocardial infarction	NCCIH

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Table 6-1. Ongoing Studies on Lead (Pb)

Investigator	Affiliation	Research description	Sponsor
Lu, Q	Harvard School of Public Health	Study in children to evaluate SPP1 upregulation as a critical mechanism linking Pb exposure with neural stem cell function and neurodevelopment in children	NIEHS
Papautsky, I	University of Illinois at Chicago	Longitudinal study to evaluate the relationship between PbB and functional gait and static and dynamic balance in an adolescent cohort	NIEHS
Reuben, A	Duke University	Longitudinal birth cohort study of neuroimaging data to determine whether childhood Pb exposure relates to degenerative alterations in neural structure or function by late midlife	NIEHS
Upton, K	Michigan State University	Prospective cohort study to evaluate the association between PbB and uterine fibroid tumors	NINR
Wang, G	Johns Hopkins University	Prospective birth cohort study to evaluate the relationship between PbB and placental pathology and cardiometabolic outcomes in childhood	NIEHS
Weuve, J	Boston University Medical Campus	Pilot study to evaluate XRF energy-dispersed X-ray fluorescence measurement of Pb in bone and toenails	NIEHS

NCCIH = National Center for Complementary and Integrative Health; NIEHS = National Institute of Environmental Health Sciences; NINR = National Institute of Nursing Research; PbB = blood lead concentration; SSP1 = secreted phosphoprotein 1; XRF = X-ray fluorescence

Source: NIH Reporter 2020 (<https://projectreporter.nih.gov/reporter.cfm>)

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding lead in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for Pb. As discussed in Appendix A, no MRLs were derived for Pb.

Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
Air			
EPA	RfC	Not evaluated	IRIS 2002 , 2004
EPA	NAAQS	0.15 µg/m ³ ^a	EPA 2019b
WHO	Air quality guidelines	Not listed	WHO 2010
Water & Food			
EPA	Drinking water standards and health advisories	No data	EPA 2018c
	National primary drinking water regulations for inorganic lead		EPA 2009
	MCL or TT	TT ^b	
	Action level	0.015 mg/L	
	Public health goal	zero	
	Lead and copper rule proposal		EPA 2019a
	Trigger level (proposed)	10 µg/L ^c	
	RfD		
	Tetraethyl lead	1x10 ⁻⁷ mg/kg/day	IRIS 2002
WHO	Drinking water quality guidelines		WHO 2017
	Provisional guideline value, lead	0.01 mg/L (10 µg/L) ^d	
FDA	Substances Added to Food ^e	Not listed	FDA 2019a
	Allowable level of lead in bottled water	0.005 mg/L	FDA 2019b

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Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
Cancer			
HHS	Carcinogenicity classification Lead and lead compounds	Reasonably anticipated to be human carcinogens	NTP 2016
EPA	Carcinogenicity classification Lead and compounds (inorganic)	B2 ^f	IRIS 2004
IARC	Carcinogenicity classification Lead	Group 2B ^g	IARC 1987 , 2019
	Lead compounds, inorganic	Group 2A ^h	IARC 2006 , 2019
	Lead compounds, organic	Group 3 ⁱ	IARC 2006 , 2019
Occupational			
OSHA	PEL (8-hour TWA) for general industry Lead (elemental, inorganic and organic soaps)	50 µg/m ³	OSHA 2019a
	Tetraethyl lead and tetramethyl lead	0.075 mg/m ³ ^j	OSHA 2019b
	PEL (8-hour TWA) for construction and shipyards Lead (elemental, inorganic and organic soaps)	50 µg/m ³	OSHA 2019c , 2019a
	Tetraethyl lead	0.1 mg/m ³ ^j	OSHA 2019d , 2019e
	Tetramethyl lead	0.15 mg/m ³ ^j	OSHA 2019d , 2019f
	Action level (8-hour TWA) for general industry, construction Lead (elemental, inorganic and organic soaps)	30 µg/m ³	OSHA 2019a , 2019c
	Medical removal protection for general industry Temporary removal blood lead level	≥60 µg/100 g	OSHA 2019a
	Return to work blood lead level	<40 µg/100 g	
	Medical removal protection for construction and shipyards Temporary removal blood lead level	≥50 µg/dL	OSHA 2019c
	Return to work blood lead level	<40 µg/dL	
NIOSH	REL (8-hour TWA) Lead and compounds (as Pb)	0.05 mg/m ³	NIOSH 2019a
	Tetraethyl lead (as Pb) and tetramethyl lead (as Pb)	0.075 mg/m ³ ^j	NIOSH 2019b , 2019c
	IDLH Lead and compounds (as Pb)	100 mg/m ³	NIOSH 2019a
	Tetraethyl lead (as Pb) and tetramethyl lead (as Pb)	40 mg/m ³	NIOSH 2019b , 2019c

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Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
Emergency Criteria			
EPA	AEGLs-air	No data	EPA 2018c
DOE	PACs-air ^k		DOE 2018a
	Lead		
	PAC-1	0.15 mg/m ³	
	PAC-2	120 mg/m ³	
	PAC-3	700 mg/m ³	
	Tetraethyl lead		
	PAC-1	0.3 mg/m ³	
	PAC-2	4 mg/m ³	
	PAC-3	40 mg/m ³	
	Tetramethyl lead		
	PAC-1	0.45 mg/m ³	
	PAC-2	4 mg/m ³	
	PAC-3	40 mg/m ³	
	Lead acetate		
	PAC-1	5 mg/m ³	
	PAC-2	55 mg/m ³	
	PAC-3	330 mg/m ³	
	Lead carbonate		
	PAC-1	0.19 mg/m ³	
	PAC-2	24 mg/m ³	
	PAC-3	900 mg/m ³	
	Lead dioxide and lead sulfide		
	PAC-1	0.17 mg/m ³	
	PAC-2	140 mg/m ³	
	PAC-3	810 mg/m ³	
	Lead tetroxide		
	PAC-1	0.17 mg/m ³	
	PAC-2	130 mg/m ³	
	PAC-3	770 mg/m ³	
	Lead sulfide		
	PAC-1	0.17 mg/m ³	
	PAC-2	140 mg/m ³	
	PAC-3	810 mg/m ³	
	Lead oxide		
	PAC-1	0.16 mg/m ³	
	PAC-2	130 mg/m ³	
	PAC-3	750 mg/m ³	

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Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
	Lead sulfate		
	PAC-1	0.22 mg/m ³	
	PAC-2	170 mg/m ³	
	PAC-3	1,000 mg/m ³	
	Lead phosphate		
	PAC-1	0.2 mg/m ³	
	PAC-2	150 mg/m ³	
	PAC-3	910 mg/m ³	
	Lead chloride		
	PAC-1	0.2 mg/m ³	
	PAC-2	160 mg/m ³	
	PAC-3	940 mg/m ³	
	Lead chromate		
	PAC-1	0.036 mg/m ³	
	PAC-2	16 mg/m ³	
	PAC-3	97 mg/m ³	
	Lead bromide		
	PAC-1	0.27 mg/m ³	
	PAC-2	200 mg/m ³	
	PAC-3	1,200 mg/m ³	
	Lead nitrate		
	PAC-1	0.24 mg/m ³	
	PAC-2	180 mg/m ³	
	PAC-3	1,100 mg/m ³	
	Lead iodide		
	PAC-1	0.33 mg/m ³	
	PAC-2	270 mg/m ³	
	PAC-3	1,600 mg/m ³	
	Lead fluoroborate		
	PAC-1	0.28 mg/m ³	
	PAC-2	220 mg/m ³	
	PAC-3	1,300 mg/m ³	
Miscellaneous Federal Guidance			
CDC	PbB reference value	5 µg/dL	CDC 2012d , 2012e
EPA	Dust-lead hazard standards		EPA 2019c
	Floors	10 µg/ft ²	
	Window sills	100 µg/ft ²	

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Table 7-1. Regulations and Guidelines Applicable to Lead (Pb)

Agency	Description	Information	Reference
EPA	Soil screening level	400 ppm	EPA 1994e, 1998 ; 2016d
HUD	Dust lead hazard action levels		HUD 2017
	Floors	$\geq 10 \mu\text{g}/\text{ft}^2$	
	Window sills	$\geq 100 \mu\text{g}/\text{ft}^2$	
	Dust lead clearance action levels		
	Interior floors	$< 10 \mu\text{g}/\text{ft}^2$	
	Porch floors	$< 40 \mu\text{g}/\text{ft}^2$	
	Window sills	$< 100 \mu\text{g}/\text{ft}^2$	
	Window troughs	$< 100 \mu\text{g}/\text{ft}^2$	

^aNot-to-exceed air Pb concentration of $0.15 \mu\text{g}/\text{m}^3$ in total suspended solids for a 3-month rolling average, evaluated over a 3-year period (i.e., the 3-month rolling average cannot exceed $0.15 \mu\text{g}/\text{m}^3$ over a 3-year period).

^bIf >10% of tap water samples exceed the action level, a water system must take additional steps to control the corrosiveness of its water.

^cExceedance would trigger additional planning, monitoring, and treatment requirements, which vary depending on the characteristics of the water system.

^dThe guideline value is designated as provisional on the basis of treatment performance and analytical achievability because it is extremely difficult to achieve a lower concentration by central conditioning, such as phosphate dosing.

^eThe Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."

^fGroup B2: probable human carcinogen.

^gGroup 2B: possibly carcinogenic to humans.

^hGroup 2A: probably carcinogenic to humans.

ⁱGroup 3: not classifiable as to carcinogenicity to humans.

^jSkin designation.

^kDefinitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; CDC = Centers for Disease Control and Prevention; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; HUD = Housing and Urban Development; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentration; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MCL = maximum contaminant level; NAAQS = National Ambient Air Quality Standard; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PbB = blood lead concentration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TT = treatment technique; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥ 365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children. Effects are diverse and exposure to Pb is associated with toxicity to every organ system. For the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental), effects occur at the lowest PbBs studied (≤ 5 $\mu\text{g/dL}$). Exposure thresholds for effects on specific organ systems have not been identified (i.e., no safe level has been identified). Cognitive deficits in children occurring at the lowest PbBs (≤ 5 $\mu\text{g/dL}$) are the best substantiated effects. However, because the lowest PbBs are associated with serious adverse effects (e.g., declining cognitive function in children), MRLs for Pb have not been derived.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR LEAD

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to Pb.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for Pb. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of Pb have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of Pb are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects

Species

Human

Laboratory mammals

Route of exposure

Inhalation

Oral

Dermal (or ocular)

Parenteral (these studies will be considered supporting data)

Health outcome

Death

Systemic effects

Body weight effects

Respiratory effects

Cardiovascular effects

Gastrointestinal effects

Hematological effects

Musculoskeletal effects

Hepatic effects

Renal effects

Dermal effects

Ocular effects

Endocrine effects

Immunological effects

Neurological effects

Reproductive effects

Developmental effects

Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for Pb released for public comment in 2019; thus, the literature search was restricted to studies published between February 2015 and September 2019. The following main databases were searched in September 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for Pb. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to Pb were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database	search date	Query string
PubMed		
09/2019		(((((10031-22-8[rn] OR 10099-74-8[rn] OR 10101-63-0[rn] OR 11119-70-3[rn] OR 12709-98-7[rn] OR 1309-60-0[rn] OR 1314-41-6[rn] OR 1314-87-0[rn] OR 1317-36-8[rn] [13424-46-9[rn] OR 13814-96-5[rn] OR 15245-44-0[rn] OR 16040-38-3[rn] OR 39377-56-5[rn] OR 598-63-0[rn] OR 7439-92-1[rn] OR 7446-14-2[rn] OR 7446-27-7[rn] OR 7758-95-4[rn] OR 7758-97-6[rn] OR 78-00-2[rn] OR 301-04-2[rn]) AND (((("Lead/toxicity"[mh] OR "Lead/adverse effects"[mh] OR "Lead/poisoning"[mh] OR "Lead/pharmacokinetics"[mh]) OR ("Lead"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Lead"[mh] AND toxicokinetics[mh:noexp]) OR ("Lead/blood"[mh] OR "Lead/cerebrospinal fluid"[mh] OR "Lead/urine"[mh]) OR ("Lead"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Lead"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Lead/antagonists and inhibitors"[mh]) OR ("Lead/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Lead"[majr] AND cancer[sb]) OR ("Lead/pharmacology"[majr])) AND (2016/02/01 : 3000[mhda] OR 2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])) OR ("lead poisoning"[mh] AND (2016/02/01 : 3000[mhda] OR 2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])) OR (((("Tetraethyl Lead/toxicity"[mh] OR "Tetraethyl Lead/adverse effects"[mh] OR "Tetraethyl Lead/poisoning"[mh] OR "Tetraethyl Lead/pharmacokinetics"[mh]) OR ("Tetraethyl Lead"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Tetraethyl Lead"[mh] AND toxicokinetics[mh:noexp]) OR ("Tetraethyl Lead/blood"[mh] OR "Tetraethyl Lead/cerebrospinal fluid"[mh] OR "Tetraethyl Lead/urine"[mh]) OR ("Tetraethyl Lead"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Tetraethyl Lead"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR

APPENDIX B

Table B-2. Database Query Strings

Database	search date	Query string
		"transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Tetraethyl Lead/antagonists and inhibitors"[mh]) OR ("Tetraethyl Lead/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Tetraethyl Lead"[majr] AND cancer[sb]) OR ("Tetraethyl Lead/pharmacology"[majr])) AND (2016/02/01 : 3000[mhda] OR 2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])) OR ((301-04-2[m] AND ("Organometallic Compounds/toxicity"[mh] OR "Organometallic Compounds/adverse effects"[mh] OR "Organometallic Compounds/poisoning"[mh] OR "Organometallic Compounds/pharmacokinetics"[mh]) OR ("Organometallic Compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Organometallic Compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("Organometallic Compounds/blood"[mh] OR "Organometallic Compounds/cerebrospinal fluid"[mh] OR "Organometallic Compounds/urine"[mh]) OR ("Organometallic Compounds"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Organometallic Compounds"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Organometallic Compounds/antagonists and inhibitors"[mh] OR ("Organometallic Compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Organometallic Compounds"[majr] AND cancer[sb]) OR ("Organometallic Compounds/pharmacology"[majr])) AND (2016/02/01 : 3000[mhda] OR 2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])) OR (((1,3-Benzenediol, 2,4,6-trinitro-, lead(2+) salt"[tw] OR "Borate(1-), tetrafluoro-, lead (2+) "[tw] OR "Borate(1-), tetrafluoro-, lead(2+) "[tw] OR "Chromic acid lead salt with lead molybdate"[tw] OR "Chromic acid, lead and molybdenum salt"[tw] OR "Chromium lead molybdenum oxide"[tw] OR "Lead (II) iodide"[tw] OR "Lead 2,4,6-trinitro-m-phenylene dioxide"[tw] OR "Lead bis(tetrafluoroborate)"[tw] OR "Lead borofluoride"[tw] OR "Lead boron fluoride"[tw] OR "Lead Brown"[tw] OR "Lead chromate molybdate"[tw] OR "lead diiodide"[tw] OR "Lead dioxide"[tw] OR "Lead fluoborate"[tw] OR "Lead fluoroborate"[tw] OR "Lead iodide"[tw] OR "Lead molybdate chromate"[tw] OR "Lead molybdenum chromate"[tw] OR "Lead oxide"[tw] OR "Lead peroxide"[tw] OR "Lead styphnate"[tw] OR "Lead superoxide"[tw] OR "Lead tetrafluoroborate"[tw] OR "Lead trichlorate"[tw] OR "Lead trinitroresorcinate"[tw] OR "Lead(II) iodide"[tw] OR "Lead(II) styphnate"[tw] OR "Lead(II) tetrafluoroborate"[tw] OR "Lead(IV) oxide"[tw] OR "Lead-molybdenum chromate"[tw] OR "Molybdenum-lead chromate"[tw] OR "Plumbic oxide"[tw] OR "Plumbous iodide"[tw] OR "Plumbum iodatum"[tw] OR "Resorcinol, 2,4,6-trinitro-, lead(2+) salt"[tw] OR "Thiolead A"[tw] OR "Tricinat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine

Table B-2. Database Query Strings

Database	search date	Query string
		disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic"[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR (me[sh] AND ("humans"[mh] OR "animals"[mh]))) AND (2016/02/01 : 3000[mhda] OR 2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])) OR (("Plumbism"[tw] OR "saturnism"[tw] OR "colica pictorum"[tw] OR "Devon colic"[tw] OR "painter's colic"[tw]) NOT "lead poisoning"[mh]) OR (((("1,3-Benzenediol, 2,4,6-trinitro-, lead(2+) salt (1:1)"[tw] OR "Acetic acid lead(2+) salt"[tw] OR "Acetic acid, lead salt"[tw] OR "Acetic acid, lead(2+) salt"[tw] OR "Acetic acid, lead(2+) salt"[tw] OR "Anglislite"[tw] OR "Azarcon"[tw] OR "Borate(1-), tetrafluoro-, lead (2+)"[tw] OR "Borate(1-), tetrafluoro-, lead(2+) (2:1)"[tw] OR "C.I. Pigment Metal 4"[tw] OR "C.I. Pigment Yellow 46"[tw] OR "CARBONIC ACID, LEAD SALT (1:1)"[tw] OR "Carbonic acid, lead salt (2+) (1:1)"[tw] OR "Carbonic acid, lead(2+) salt"[tw] OR "Cerussete"[tw] OR "Cerussite"[tw] OR "Chrome Orange"[tw] OR "Chrome Yellow"[tw] OR "Chromic acid (H2CrO4), lead(2+) salt (1:1)"[tw] OR "Chromic acid lead salt"[tw] OR "CHROMIC ACID, LEAD (2+) SALT (1:1)"[tw] OR "Chromic Acid, Lead (II) Salt (1:1)"[tw] OR "Chromic acid, lead and molybdenum salt"[tw] OR "Chromic acid, lead salt"[tw] OR "Chromic acid, lead(2+) salt (1:1)"[tw] OR "Chromium lead molybdenum oxide"[tw] OR "Chromium lead oxide"[tw] OR "CI pigment metal 4"[tw] OR "CI Pigment Yellow 46"[tw] OR "Collodial lead phosphate"[tw] OR "Dibasic lead acetate"[tw] OR "Dibasic lead carbonate"[tw] OR "Dibasic lead sulfate"[tw] OR "Entan"[tw] OR "Fast White"[tw] OR "Flowsperse R 12"[tw] OR "Freemans White Lead"[tw] OR "Galena"[tw] OR "Glover"[tw] OR "Gold Satinobre"[tw] OR "Heuconin 5"[tw] OR "Lead (II) carbonate"[tw] OR "Lead (II) chloride"[tw] OR "Lead (II) chromate"[tw] OR "Lead (II) iodide"[tw] OR "Lead (II) nitrate"[tw] OR "Lead (II) oxide"[tw] OR "Lead (II) sulfate"[tw] OR "Lead (II) sulfide"[tw] OR "Lead (II, IV) oxide"[tw] OR "Lead (IV) oxide"[tw] OR "Lead 2,4,6-trinitro-m-phenylene dioxide"[tw] OR "Lead acetate"[tw] OR "Lead azide"[tw] OR "Lead bis(tetrafluoroborate)"[tw] OR "Lead borofluoride"[tw] OR "Lead boron fluoride"[tw] OR "Lead Bottoms"[tw] OR "Lead bromide"[tw] OR "Lead brown"[tw] OR "Lead carbonate"[tw] OR "Lead chloride"[tw] OR "Lead chromate"[tw] OR "Lead chromate(VI)"[tw] OR "Lead chromium oxide (PbCrO4)"[tw] OR "Lead di(acetate)"[tw] OR "Lead diacetate"[tw] OR "Lead diazide"[tw] OR "Lead dibasic acetate"[tw] OR "Lead dibromide"[tw] OR "Lead dichloride"[tw] OR "Lead diiodide"[tw] OR "Lead dinitrate"[tw] OR "Lead dioxide"[tw] OR "Lead element"[tw] OR "Lead flake"[tw] OR "Lead fluoborate"[tw] OR "Lead fluoroborate"[tw] OR "Lead iodide"[tw] OR "Lead metal"[tw] OR "Lead molybdate chromate"[tw] OR "Lead molybdenum chromate"[tw] OR "Lead monoxide"[tw] OR "Lead monosulfate"[tw] OR "Lead monosulfide"[tw] OR "Lead monoxide"[tw] OR "Lead nitrate"[tw] OR "Lead orthophosphate"[tw] OR "Lead orthoplumbate"[tw] OR "Lead oxide"[tw] OR "Lead peroxide"[tw] OR "Lead phosphate"[tw] OR "Lead protoxide"[tw] OR "Lead S 2"[tw] OR "Lead S2"[tw] OR "Lead styphnate"[tw] OR "Lead sulfate"[tw] OR "Lead sulfide"[tw] OR "Lead sulphate"[tw] OR "Lead sulphide"[tw] OR "Lead superoxide"[tw] OR "Lead tetraethide"[tw] OR "Lead tetraethyl"[tw] OR "Lead tetrafluoroborate"[tw] OR "Lead tetraoxide"[tw] OR "Lead tetroxide"[tw] OR "Lead tricate"[tw] OR "Lead

Table B-2. Database Query Strings

Database search date	Query string
	<p>trinitoresorcinat[tw] OR "Lead(+2) sulfate"[tw] OR "Lead(2+) acetate"[tw] OR "Lead(2+) azide"[tw] OR "Lead(2+) bis(nitrate)"[tw] OR "Lead(2+) bromide"[tw] OR "Lead(2+) carbonate"[tw] OR "Lead(2+) chloride"[tw] OR "Lead(2+) nitrate"[tw] OR "Lead(2+) oxide"[tw] OR "Lead(2+) phosphate"[tw] OR "Lead(2+) phosphate (Pb3(PO4)2)"[tw] OR "Lead(2+) salt carbamic acid (1:1)"[tw] OR "Lead(2+) sulfate"[tw] OR "Lead(2+) sulfide"[tw] OR "Lead(II) acetate"[tw] OR "Lead(II) azide"[tw] OR "Lead(II) bromide"[tw] OR "Lead(II) carbonate"[tw] OR "Lead(II) chloride"[tw] OR "Lead(II) chromate"[tw] OR "Lead(II) dinitrate"[tw] OR "Lead(II) iodide"[tw] OR "Lead(II) nitrate"[tw] OR "Lead(II) oxide"[tw] OR "Lead(II) phosphate"[tw] OR "Lead(II) phosphate (3:2)"[tw] OR "Lead(II) styphnate"[tw] OR "Lead(II) sulfate"[tw] OR "Lead(II) sulfide"[tw] OR "Lead(II) tetrafluoroborate"[tw] OR "Lead(IV) oxide"[tw] OR "Lead, elemental"[tw] OR "Lead, inorganic"[tw] OR "Lead, tetraethyl"[tw] OR "Lead, tetraethyl-"[tw] OR "Lead-molybdenum chromate"[tw] OR "Litharge"[tw] OR "Massicot"[tw] OR "Massicotite"[tw] OR "Mennige"[tw] OR "Milk White"[tw] OR "mine orange"[tw] OR "Mineral Orange"[tw] OR "Mineral red"[tw] OR "minio anaranjado"[tw] OR "Minium"[tw] OR "Molybdenum-lead chromate"[tw] OR "Mulhouse White"[tw] OR "Nitric acid lead(2+) salt"[tw] OR "Nitric acid, lead(2+) salt"[tw] OR "Orange lead"[tw] OR "Orangemennige"[tw] OR "Paris Red"[tw] OR "PbSO4"[tw] OR "Perlex paste 500"[tw] OR "Perlex paste 600A"[tw] OR "Phoenicochroite"[tw] OR "Phosphoric acid, lead salt"[tw] OR "Phosphoric acid, lead(2+) salt (2:3)"[tw] OR "Pigment Red 105"[tw] OR "Pigment White 3"[tw] OR "Pigment Yellow 34"[tw] OR "Pigment Yellow 46"[tw] OR "Plumbane"[tw] OR "Plumbi"[tw] OR "Plumbic oxide"[tw] OR "Plumboplumbic oxide"[tw] OR "Plumbous"[tw] OR "Plumbum"[tw] OR "Red lead"[tw] OR "Resorcinol, 2,4,6-trinitro-, lead(2+) salt (1:1)"[tw] OR "Rough lead bullion"[tw] OR "Royal Yellow 6000"[tw] OR "Salt of saturn"[tw] OR "Sandix"[tw] OR "Saturn red"[tw] OR "Sugar of lead"[tw] OR "Sulfuric acid, lead(2+) salt"[tw] OR "Tetra Ethylene Lead"[tw] OR "Tetra(methylethyl)lead"[tw] OR "Tetraethyl lead"[tw] OR "Tetraethyl plumbane"[tw] OR "Tetraethyllead"[tw] OR "Tetraethyllead, liquid"[tw] OR "tetraethylplomb"[tw] OR "Tetraethylplombane"[tw] OR "Tetraethylplumbane"[tw] OR "tetraetilplomo"[tw] OR "Thiolead A"[tw] OR "Tricinat"[tw] OR "Trilead bis(orthophosphate)"[tw] OR "Trilead phosphate"[tw] OR "Trilead tetraoxide"[tw] OR "Trilead tetroxide"[tw] OR "Unichem PBA"[tw] OR "Yellow lead ocher"[tw]) NOT medline[sb]) AND (2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])))) OR (((("Lead"[ti] NOT "lead to"[ti]) OR "Pb"[ti] OR "PbS"[ti] OR "PbO"[ti]) NOT medline[sb]) AND (2016/02/01 : 3000[crdt] OR 2016/02/01 : 3000[edat] OR 2015/02/01 : 3000[dp])))</p>
Toxline	
09/2019	<p>Date limit: 2015 to present: (10031-22-8[rn] OR 10099-74-8[rn] OR 10101-63-0[rn] OR 11119-70-3[rn] OR 12709-98-7[rn] OR 1309-60-0[rn] OR 1314-41-6[rn] OR 1314-87-0[rn] OR 1317-36-8[rn] OR 13424-46-9[rn] OR 13814-96-5[rn] OR 15245-44-0[rn] OR 16040-38-3[rn] OR 39377-56-5[rn] OR 598-63-0[rn] OR 7439-92-1[rn] OR 7446-14-2[rn] OR 7446-27-7[rn] OR 7758-95-4[rn] OR 7758-97-6[rn] OR 78-00-2[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org])</p> <p>("1,3-Benzenediol, 2,4,6-trinitro-, lead(2+) salt (1:1)" OR "Acetic acid lead(2+) salt" OR "Acetic acid, lead salt" OR "Acetic acid, lead(2+) salt" OR "Acetic acid, lead(2+) salt" OR "Anglislite" OR "Azarcon" OR "Borate(1-), tetrafluoro-, lead (2+)" OR "Borate(1-), tetrafluoro-, lead(2+) (2:1)" OR "C.I. Pigment Metal 4" OR "C.I. Pigment Yellow 46" OR "CARBONIC ACID, LEAD SALT (1:1)" OR "Carbonic acid, lead salt (2+) (1:1)") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM</p>

Table B-2. Database Query Strings

Database	search date	Query string
		[org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Carbonic acid, lead(2+) salt" OR "Cerussite" OR "Cerussite" OR "Chrome Orange" OR "Chrome Yellow" OR "Chromic acid (H2CrO4), lead(2+) salt (1:1)" OR "Chromic acid lead salt" OR "CHROMIC ACID, LEAD (2+) SALT (1:1)" OR "Chromic Acid, Lead (II) Salt (1:1)" OR "Chromic acid, lead and molybdenum salt" OR "Chromic acid, lead salt" OR "Chromic acid, lead(2+) salt (1:1)" OR "Chromium lead molybdenum oxide") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Chromium lead oxide" OR "CI pigment metal 4" OR "CI Pigment Yellow 46" OR "Collodial lead phosphate" OR "Dibasic lead acetate" OR "Dibasic lead carbonate" OR "Dibasic lead sulfate" OR "Entan" OR "Fast White" OR "Flowsperse R 12" OR "Freemans White Lead" OR "Galena" OR "Glover" OR "Gold Satinobre" OR "Heuconin 5" OR "Lead (II) carbonate" OR "Lead (II) chloride" OR "Lead (II) chromate" OR "Lead (II) iodide" OR "Lead (II) nitrate" OR "Lead (II) oxide" OR "Lead (II) sulfate" OR "Lead (II) sulfide") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Lead (II,IV) oxide" OR "Lead (IV) oxide " OR "Lead 2,4,6-trinitro-m-phenylene dioxide" OR "Lead acetate" OR "Lead azide" OR "Lead bis(tetrafluoroborate)" OR "Lead borofluoride" OR "Lead boron fluoride" OR "Lead Bottoms" OR "Lead bromide" OR "Lead brown" OR "Lead carbonate" OR "Lead chloride" OR "Lead chromate" OR "Lead chromate(VI)" OR "Lead chromium oxide (PbCrO4)" OR "Lead di(acetate)") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Lead diacetate" OR "Lead diazide" OR "Lead dibasic acetate" OR "Lead dibromide" OR "Lead dichloride" OR "Lead diiodide" OR "Lead dinitrate" OR "Lead dioxide" OR "Lead element" OR "Lead flake" OR "Lead fluoborate" OR "Lead fluoroborate" OR "Lead iodide" OR "Lead metal" OR "Lead molybdate chromate" OR "Lead molybdenum chromate" OR "Lead monooxide" OR "Lead monosulfate" OR "Lead monosulfide") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Lead monoxide" OR "Lead nitrate" OR "Lead orthophosphate" OR "Lead orthoplumbate" OR "Lead oxide" OR "Lead peroxide" OR "Lead phosphate" OR "Lead protoxide" OR "Lead S 2" OR "Lead S2" OR "Lead styphnate" OR "Lead sulfate" OR "Lead sulfide" OR "Lead sulphate" OR "Lead sulphide" OR "Lead superoxide" OR "Lead tetraethide" OR "Lead tetraethyl" OR "Lead tetrafluoroborate" OR "Lead tetraoxide") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Lead tetroxide" OR "Lead trincate" OR "Lead trinitroresorcinate" OR "Lead(+2) sulfate" OR "Lead(2+) acetate" OR "Lead(2+) azide" OR "Lead(2+) bis(nitrate)" OR "Lead(2+) bromide" OR "Lead(2+) carbonate" OR "Lead(2+) chloride" OR "Lead(2+) nitrate" OR "Lead(2+) oxide" OR "Lead(2+) phosphate" OR "Lead(2+) phosphate (Pb3(PO4)2)" OR "Lead(2+) salt carbamic acid (1:1) " OR "Lead(2+) sulfate") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP

Table B-2. Database Query Strings

Database	search date	Query string
		[org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Lead(2+) sulfide" OR "Lead(II) acetate" OR "Lead(II) azide" OR "Lead(II) bromide" OR "Lead(II) carbonate" OR "Lead(II) chloride" OR "Lead(II) chromate" OR "Lead(II) dinitrate" OR "Lead(II) iodide" OR "Lead(II) nitrate" OR "Lead(II) oxide" OR "Lead(II) phosphate" OR "Lead(II) phosphate (3:2)" OR "Lead(II) styphnate" OR "Lead(II) sulfate" OR "Lead(II) sulfide" OR "Lead(II) tetrafluoroborate" OR "Lead(IV) oxide") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Lead, elemental" OR "Lead, inorganic" OR "Lead, tetraethyl" OR "Lead, tetraethyl-" OR "Lead-molybdenum chromate" OR "Litharge" OR "Massicot" OR "Massicotite" OR "Mennige" OR "Milk White" OR "mine orange" OR "Mineral Orange" OR "Mineral red" OR "minio anaranjado" OR "Minium" OR "Molybdenum-lead chromate" OR "Mulhouse White" OR "Nitric acid lead(2+) salt" OR "Nitric acid, lead(2+) salt") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Orange lead" OR "Orangemennige" OR "Paris Red" OR "PbSO4" OR "Perlex paste 500" OR "Perlex paste 600A" OR "Phoenicochroite" OR "Phosphoric acid, lead salt" OR "Phosphoric acid, lead(2+) salt (2:3)" OR "Pigment Red 105" OR "Pigment White 3" OR "Pigment Yellow 34" OR "Pigment Yellow 46" OR "Plumbane" OR "Plumbi" OR "Plumbic oxide" OR "Plumboplumbic oxide" OR "Plumbous" OR "Plumbum") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Red lead" OR "Resorcinol, 2,4,6-trinitro-, lead(2+) salt (1:1)" OR "Rough lead bullion" OR "Royal Yellow 6000" OR "Salt of saturn" OR "Sandix" OR "Saturn red" OR "Sugar of lead" OR "Sulfuric acid, lead(2+) salt" OR "Tetra Ethylene Lead" OR "Tetra(methylethyl)lead" OR "Tetraethyl lead" OR "Tetraethyl plumbane" OR "Tetraethyllead" OR "Tetraethyllead, liquid" OR "tetraethylplomb") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) ("Tetraethylplumbane" OR "Tetraethylplumbane" OR "tetraetilplomo" OR "Thiolead A" OR "Tricinat" OR "Trilead bis(orthophosphate)" OR "Trilead phosphate" OR "Trilead tetraoxide" OR "Trilead tetroxide" OR "Unichem PBA" OR "Yellow lead ocher") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) Term searched as exact words: "lead" AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) Date limit: 2013 to present: "Plumbism" OR "saturnism" OR "colica pictorum" OR "Devon colic" OR "painter's colic"
Toxcenter		
09/2019	L1	8918 SEA 10031-22-8 OR 10099-74-8 OR 10101-63-0 OR 11119-70-3 OR

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Table B-2. Database Query Strings

Database search date	Query string
	12709-98-7 OR 1309-60-0 OR 1314-41-6 OR 1314-87-0 OR 1317-36-8 OR 13424-46-9
L2	239150 SEA 13814-96-5 OR 15245-44-0 OR 16040-38-3 OR 301-04-2 OR 39377-56-5 OR 598-63-0 OR 7439-92-1 OR 7446-14-2 OR 7446-27-7 OR 7758-95-4 OR 7758-97-6 OR 78-00-2
L3	244612 SEA L1 OR L2
L4	244408 SEA L3 NOT TSCATS/FS
L5	225905 SEA L4 NOT PATENT/DT
L6	26519 SEA L5 AND ED>=20160201 ACT TOXQUERY/Q
L7	----- QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
L8	QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPB OR EPIDEMIOLOGY/ST,CT, IT)
L9	QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
L10	QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
L11	QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
L12	QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
L13	QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
L14	QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
L15	QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
L16	QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
L17	QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
L18	QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
L19	QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
L20	QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
L21	QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
L22	QUE (ENDOCRIN? AND DISRUPT?)
L23	QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
L24	QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
L25	QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
L26	QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER? OR NEOPLAS?)
L27	QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
L28	QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
L29	QUE (NEPHROTOX? OR HEPATOTOX?)
L30	QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
L31	QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
L32	QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
L33	QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
L34	QUE (MARMOSSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L35	QUE L32 OR L33 OR L34
L36	QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR

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Table B-2. Database Query Strings

Database search date	Query string
	PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 -----
L38	14067 SEA L6 AND L37
L39	2663 SEA L38 AND MEDLINE/FS
L40	4980 SEA L38 AND BIOSIS/FS
L41	6411 SEA L38 AND CAPLUS/FS
L42	13 SEA L38 NOT (L39 OR L40 OR L41)
L43	11438 DUP REM L39 L40 L42 L41 (2629 DUPLICATES REMOVED) ANSWERS '1-11438' FROM FILE TOXCENTER
L*** DEL	2663 S L38 AND MEDLINE/FS
L*** DEL	2663 S L38 AND MEDLINE/FS
L44	2663 SEA L43
L*** DEL	4980 S L38 AND BIOSIS/FS
L*** DEL	4980 S L38 AND BIOSIS/FS
L45	3952 SEA L43
L*** DEL	6411 S L38 AND CAPLUS/FS
L*** DEL	6411 S L38 AND CAPLUS/FS
L46	4810 SEA L43
L*** DEL	13 S L38 NOT (L39 OR L40 OR L41)
L*** DEL	13 S L38 NOT (L39 OR L40 OR L41)
L47	13 SEA L43
L48	8775 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS SAVE TEMP L48 LEAD/A

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView 09/2019	Compounds searched: 10031-22-8; 10099-74-8; 10101-63-0; 11119-70-3; 12709-98-7; 1309-60-0; 1314-41-6; 1314-87-0; 1317-36-8; 13424-46-9; 13814-96-5; 15245-44-0; 16040-38-3; 301-04-2; 39377-56-5; 598-63-0; 7439-92-1; 7446-14-2; 7446-27-7; 7758-95-4; 7758-97-6; 78-00-2
NTP 09/2019	NTP Site Search (http://ntpsearch.niehs.nih.gov/home), date limit 2015 to present: "10031-22-8" "10099-74-8" "10101-63-0" "11119-70-3" "12709-98-7" "1309-60-0" "1314-41-6" "1314-87-0" "1317-36-8" "13424-46-9" "13814-96-5" "15245-44-0" "16040-38-3" "301-04-2" "39377-56-5" "598-63-0" "7439-92-1" "7446-14-2" "7446-27-7" "7758-95-4" "7758-97-6" "78-00-2" Limited to content types reports & publications; systematic reviews; ROC profiles, reviews, or candidates; or testing status, date limit 2015 to present: "lead"
Regulations.gov 10/2019	Compounds searched: 10031-22-8; 10099-74-8; 10101-63-0; 11119-70-3; 12709-98-7; 1309-60-0; 1314-41-6; 1314-87-0; 1317-36-8; 13424-46-9; 13814-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	96-5; 15245-44-0; 16040-38-3; 301-04-2; 39377-56-5; 598-63-0; 7439-92-1; 7446-14-2; 7446-27-7; 7758-95-4; 7758-97-6; 78-00-2
NIH RePORTER 01/2020	<p>Search in: Projects AdminIC: All, Fiscal Year: Active Projects Text Search (Advanced):</p> <p>"1,3-Benzenediol, 2,4,6-trinitro-, lead" OR "Acetic acid lead " OR "Acetic acid, lead salt" OR "Acetic acid, lead " OR "Acetic acid, lead " OR "Anglislite" OR "Azarcon" OR "Borate(1-), tetrafluoro-, lead" OR "Borate(1-), tetrafluoro-, lead" OR "C.I. Pigment Metal 4" OR "C.I. Pigment Yellow 46" OR "CARBONIC ACID, LEAD SALT" OR "Carbonic acid, lead salt" OR "Carbonic acid, lead" OR "Cerussite" OR "Cerussite" OR "Chrome Orange" OR "Chrome Yellow" OR "Chromic acid (H₂CrO₄), lead" OR "Chromic acid lead salt " OR "CHROMIC ACID, LEAD" OR "Chromic Acid, Lead (II) Salt" OR "Chromic acid, lead and molybdenum salt" OR "Chromic acid, lead salt" OR "Chromic acid, lead" OR "Chromium lead molybdenum oxide" OR "Chromium lead oxide" OR "CI pigment metal 4" OR "CI Pigment Yellow 46" OR "Collodial lead phosphate" OR "Dibasic lead acetate" OR "Dibasic lead carbonate" OR "Dibasic lead sulfate" OR "Entan" OR "Fast White" OR "Flowsperse R 12" OR "Freemans White Lead" OR "Galena" OR "Glover" OR "Gold Satinobre" OR "Heuconin 5" OR "Lead (II) carbonate" OR "Lead (II) chloride" OR "Lead (II) chromate" OR "Lead (II) iodide" OR "Lead (II) nitrate" OR "Lead (II) oxide" OR "Lead (II) sulfate" OR "Lead (II) sulfide" OR "Lead (II, IV) oxide" OR "Lead (IV) oxide " OR "Lead 2,4,6-trinitro-m-phenylene dioxide" OR "Lead acetate" OR "Lead azide" OR "Lead bis(tetrafluoroborate)" OR "Lead borofluoride" OR "Lead boron fluoride" OR "Lead Bottoms" OR "Lead bromide" OR "Lead brown" OR "Lead carbonate" OR "Lead chloride" OR "Lead chromate" OR "Lead chromate(VI)" OR "Lead chromium oxide (PbCrO₄)" OR "Lead di(acetate)" OR "Lead diacetate" OR "Lead diazide" OR "Lead dibasic acetate" OR "Lead dibromide" OR "Lead dichloride" OR "Lead diiodide" OR "Lead dinitrate" OR "Lead dioxide" OR "Lead element" OR "Lead flake" OR "Lead fluoborate" OR "Lead fluoroborate" OR "Lead iodide" OR "Lead metal" OR "Lead molybdate chromate" OR "Lead molybdenum chromate" OR "Lead monooxide" OR "Lead monosulfate" OR "Lead monosulfide" OR "Lead monoxide" OR "Lead nitrate" OR "Lead orthophosphate" OR "Lead orthoplumbate" OR "Lead oxide" OR "Lead peroxide" OR "Lead phosphate" OR "Lead protoxide" OR "Lead S 2" OR "Lead S2" OR "Lead styphnate" OR "Lead sulfate" OR "Lead sulfide" OR "Lead sulphate" OR "Lead sulphide" OR "Lead superoxide" OR "Lead tetraethide" OR "Lead tetraethyl"</p> <p>"Lead tetrafluoroborate" OR "Lead tetraoxide" OR "Lead tetroxide" OR "Lead tricate" OR "Lead trinitroresorcinate" OR "Lead(II) acetate" OR "Lead(II) azide" OR "Lead(II) bromide" OR "Lead(II) carbonate" OR "Lead(II) chloride" OR "Lead(II) chromate" OR "Lead(II) dinitrate" OR "Lead(II) iodide" OR "Lead(II) nitrate" OR "Lead(II) oxide" OR "Lead(II) phosphate" OR "Lead(II) phosphate" OR "Lead(II) styphnate" OR "Lead(II) sulfate" OR "Lead(II) sulfide" OR "Lead(II) tetrafluoroborate" OR "Lead(IV) oxide" OR "Lead, elemental" OR "Lead, inorganic" OR "Lead, tetraethyl" OR "Lead, tetraethyl-" OR "Lead-molybdenum chromate" OR "Litharge" OR "Massicot" OR "Massicotite" OR "Mennige" OR "Milk White" OR "mine orange" OR "Mineral Orange" OR "Mineral red" OR "minio anaranjado" OR "Minium" OR "Molybdenum-lead chromate" OR "Mulhouse White" OR "Nitric acid lead" OR "Nitric acid, lead" OR "Orange lead" OR "Orangemennige" OR "Paris Red" OR "PbSO₄" OR "Perlex</p>

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	<p>paste 500" OR "Perlex paste 600A" OR "Phoenicochroite" OR "Phosphoric acid, lead salt" OR "Phosphoric acid, lead" OR "Pigment Red 105" OR "Pigment White 3" OR "Pigment Yellow 34" OR "Pigment Yellow 46" OR "Plumbane" OR "Plumbi" OR "Plumbic oxide" OR "Plumboplumbic oxide" OR "Plumbous" OR "Plumbum" OR "Red lead" OR "Resorcinol, 2,4,6-trinitro-, lead" OR "Rough lead bullion" OR "Royal Yellow 6000" OR "Salt of saturn" OR "Sandix" OR "Saturn red" OR "Sugar of lead" OR "Sulfuric acid, lead" OR "Tetra Ethylene Lead" OR "Tetra(methylethyl)lead" OR "Tetraethyl lead" OR "Tetraethyl plumbane" OR "Tetraethyllead" OR "Tetraethyllead, liquid" OR "tetraethylplomb" OR "Tetraethylplombane" OR "Tetraethylplumbane" OR "tetraetilplomo" OR "Thiolead A" OR "Tricinat" OR "Trilead bis(orthophosphate)" OR "Trilead phosphate" OR "Trilead tetraoxide" OR "Trilead tetroxide" OR "Unichem PBA" OR "Yellow lead ocher" OR "Lead(2) sulfate" OR "Lead(2) acetate" OR "Lead(2) azide" OR "Lead(2) bis(nitrate)" OR "Lead(2) bromide" OR "Lead(2) carbonate" OR "Lead(2) chloride" OR "Lead(2) nitrate" OR "Lead(2) oxide" OR "Lead(2) phosphate" OR "Lead(2) phosphate (Pb3(PO4)2)" OR "Lead(2) salt carbamic acid" OR "Lead(2) sulfate" OR "Lead(2) sulfide" OR "lead poisoning" OR "Plumbism" OR "saturnism" OR "colica pictorum" OR "Devon colic" OR "painter's colic" OR "blood lead"</p> <p>Search in: Projects Limit to: Project Title, AdminIC: All, Fiscal Year: Active Projects Text Search (Advanced): "lead" not ("lead academic" or "lead optimization")</p>
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 15,240
- Number of records identified from other strategies: 107
- Total number of records to undergo literature screening: 15,347

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on Pb:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 388
- Number of studies considered relevant and moved to the next step: 388

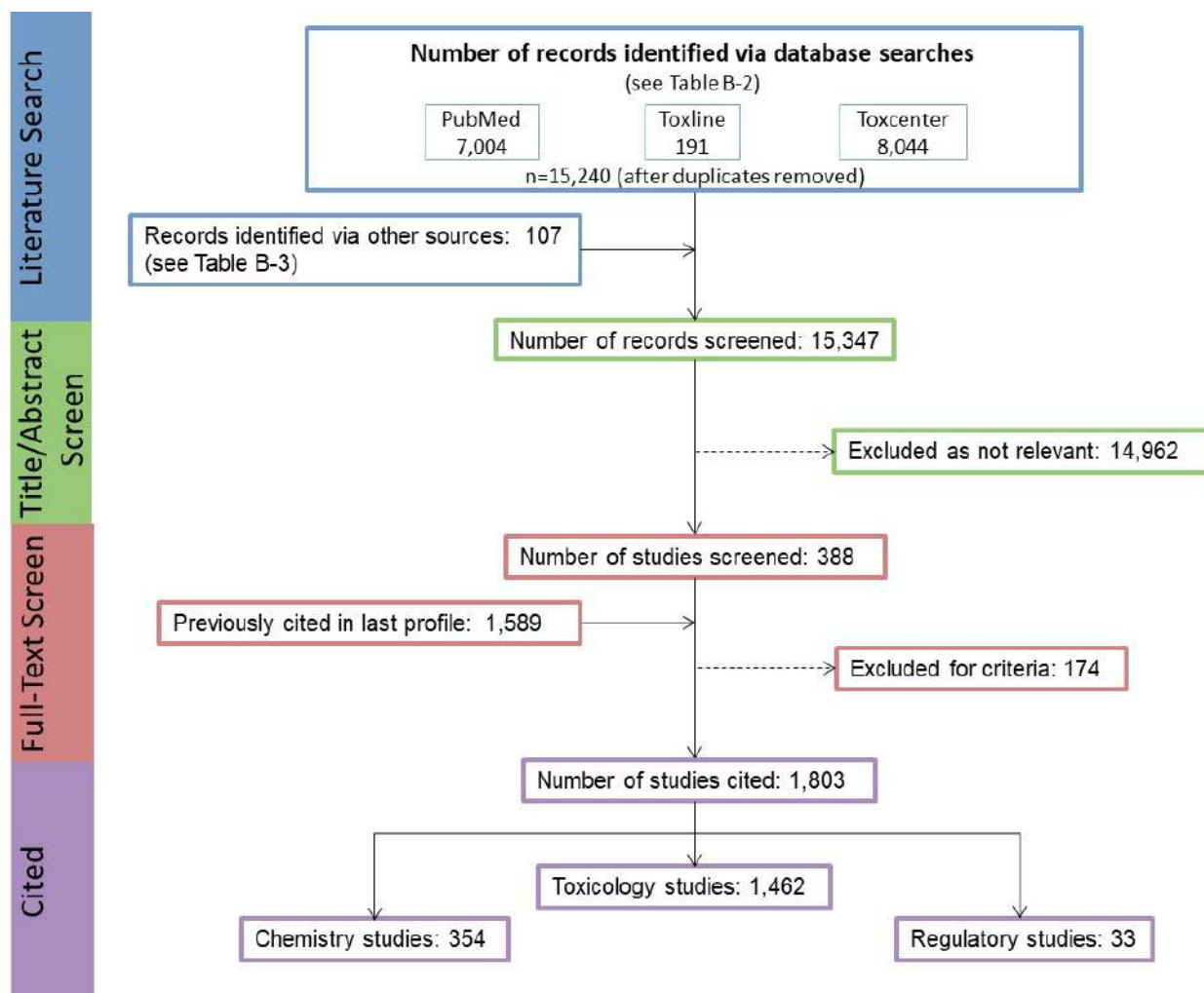
APPENDIX B

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 388
- Number of studies cited in the pre-public draft of the toxicological profile: 1,589
- Total number of studies cited in the profile: 1,803

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. September 2019 Literature Search Results and Screen for Lead (Pb)



APPENDIX C. INGESTION OF LEAD DEBRIS

The main focus of this ATSDR Toxicological Profile for Lead is on health effects of chronic low-level environmental exposures. The profile also provides information on the clinical presentation of acute Pb toxicity, which occurs when large amounts of Pb are ingested. In children, this often occurs through ingestion of paint chips containing Pb, Pb-contaminated soils, or other non-solid forms of Pb. Ingestion of solid forms of Pb (Pb debris) is a unique exposure scenario in which there is accidental or purposeful ingestion of visible debris containing Pb. This exposure may be acute (debris is expelled or removed from the body soon after ingestion) or chronic (Pb debris is retained within the body, leading to continued elevation in PbB). There are several sources of Pb debris, including Pb shot or other debris found at firing or artillery ranges, or Pb shot found in wild game meats. The information presented below reviews toxicokinetics and adverse health effects of ingested Pb debris. Information regarding the chemistry, fate, and transport of Pb debris is reviewed in Chapter 5. It should also be noted that in addition to ingestion of Pb debris, retained Pb shot or shrapnel, especially in military personnel, could contribute to elevated PbB (Gerhardsson et al. 2002; McQuirter et al. 2004); this possibility should be considered in individuals as appropriate.

Overview. No controlled studies in humans have evaluated bioavailability or toxicity of ingested Pb debris (e.g., Pb shot and other Pb-containing debris from artillery or shooting ranges). Available information is anecdotal, obtained from case reports. Thus, data are not sufficient to determine the bioavailability of ingested Pb debris or to develop dose-response relationships for toxicity. Case reports of acute exposures from ingestion of Pb debris are summarized in Table C-1; these reports demonstrate the following:

- PbB rises rapidly (within hours to a few days) following ingestion of Pb debris.
- The clinical presentation of toxicity following ingestion of Pb debris is the same as that observed for acute Pb poisoning from ingestion of other forms of Pb (see Section 2.2).
- Severity of toxicity of ingested Pb debris will depend upon how much Pb is absorbed (e.g., toxicity is related to PbB; see Section 2.2).
- The onset of toxicity can be rapid (within hours to a few days).
- Following removal of Pb debris from the body, PbBs decrease; however, applying clinical protocols for chelation therapy results in a more rapid decrease in PbB.
- Ingested Pb debris can be retained in the appendix of some individuals and continue to contribute to elevated PbB.

APPENDIX C

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Banner et al. 2012 A 15-year-old boy ingested a "handful" of Pb shot. He was admitted to the hospital for treatment 14 days after exposure.	<ul style="list-style-type: none"> Post-ingestion <ul style="list-style-type: none"> 8 days: 54 14 days: 41 Post-treatment (2 weeks): <5 	<ul style="list-style-type: none"> Most Pb was located in the appendix (14 days post-ingestion) Abdominal pain Elevated free erythrocyte protophyrin 	<ul style="list-style-type: none"> Whole bowel irrigation Appendectomy Chelation
CDC 2006 A 4-year-old boy with previously diagnosed microcephaly and mental delays ingested a metallic charm containing Pb. Time from exposure to first medical visit was not reported.	At death: 180	<ul style="list-style-type: none"> Charm was retained in the stomach (was not removed) Intractable vomiting Cerebral edema Seizures Death 	Supportive therapy
Clifton et al. 2002 A 21-month-old girl ingested Pb BB pellets. She was taken to the hospital approximately 6 hours post-ingestion.	<ul style="list-style-type: none"> Pre-ingestion (routine): 12 Post-ingestion (6 hours): 47 Post-removal of pellets: 25 Post-treatment (10 days): 16 	<ul style="list-style-type: none"> Hyperactivity No signs of neurological or gastrointestinal toxicity 	<ul style="list-style-type: none"> Bowel irrigation Colonoscopy for removal of pellets Chelation
Cox and Pesola 2005 A 73-year-old woman ingested Pb shot in game over decades.	Not reported	<ul style="list-style-type: none"> Pb shot accumulated in the appendix No information on adverse health effects was reported 	Not reported
Durlach et al. 1986 A 30-year-old man ingested Pb shot in game regularly over an unspecified period of time.	<ul style="list-style-type: none"> At initial examination: 67.4 Post-treatment <ul style="list-style-type: none"> 10 days: 52.2 13 days: 24.5 1 month: 36.8 1.5 months: 31.6 	<ul style="list-style-type: none"> Pb shot accumulated in the appendix Acute abdominal pain 	<ul style="list-style-type: none"> Bowel irritation Chelation Appendectomy

APPENDIX C

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Fergusson et al. 1997 A 4-year-old girl ingested a Pb fishing sinker. She was evaluated in the emergency room within 1 hour of ingestion.	<ul style="list-style-type: none"> • Day of ingestion: 4 • Day after ingestion: 16 	No signs of toxicity observed	Endoscopy
Gerhardsson et al. 2002 A man in his "late 40s" had retained Pb shot following a gunshot wound to the shoulder. Reconstructive surgery occurred 54 days post-accident. Some, but not all, of the Pb shot was removed during surgery.	Approximate (data presented graphically), time after accident: <ul style="list-style-type: none"> • 25 days: 28 • 50 days: 41 • 54 days (day of surgery): 55 • ~60 days: 31 • 75 days: 48 • 200 days: 36 • 375 days: 30 	<ul style="list-style-type: none"> • No signs of toxicity observed • Not all of the Pb shot could be removed during surgery 	Surgical removal of Pb pellets
Guillard et al. 2006 A 2-year-old boy ingested toy money made from pure metallic Pb.	Time post-ingestion <ul style="list-style-type: none"> • 1 day: 31.3 • 8 days: 61.1 • 1 month: 30.0 • 4 months: 24.9 • 10 months: 9.9 	<ul style="list-style-type: none"> • Development of microcytic anemia and increased blood zinc protoporphyrin • No signs of toxicity observed 	<ul style="list-style-type: none"> • Removal of object • Chelation (8 days post-ingestion)
Gustavsson and Gerhardsson 2005 A 45-year-old woman with elevated PbB was found to have Pb shot in her intestine from ingestion of game. The Pb shot was spontaneously eliminated. Time from ingestion was estimated to be sometime between 1993 and 2001.	Time of assessment: <ul style="list-style-type: none"> • January 2002: 55.0 • April 2003 (2 months post-elimination): 34.5 • November 2003: 7.2 	<ul style="list-style-type: none"> • Malaise and fatigue • "Diffuse gastrointestinal symptoms" 	No treatment (object was spontaneously eliminated)

APPENDIX C

Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Hatten et al. 2013			
<ul style="list-style-type: none"> Case 1: A 15-year-old boy ingested rifle cartridges approximately 1 month prior to evaluation. 	Case 1 <ul style="list-style-type: none"> Initial assessment: 146 19 days post-treatment: 53 3 months post-treatment: 38 	Case 1 <ul style="list-style-type: none"> Decreased activity level Vomiting, diarrhea, anorexia Hyperactive patellar and brachioradialis reflexes 	Case 1 <ul style="list-style-type: none"> Cartridges removed by endoscopy Chelation
<ul style="list-style-type: none"> Case 2: A 65-year-old woman ingested several handfuls of bullets. 	Case 2: Days after ingestion <ul style="list-style-type: none"> Day 1: 9.7 Day 2: 25.7 Day 3: 40.5 Day 60: 17.2 	Case 2 <ul style="list-style-type: none"> No signs of toxicity were observed 	Case 2 <ul style="list-style-type: none"> Endoscopy
Larsen and Blanton 2000	Not reported	<ul style="list-style-type: none"> Abdominal pain and anorexia 	Appendectomy
A 9-year-old boy ingested Pb shot in game; the Pb shot was retained in the appendix.			
Lyons and Filston 1994	<ul style="list-style-type: none"> Peak (time of assessment not reported): 23 	<ul style="list-style-type: none"> Abdominal discomfort, nausea, vomiting, diarrhea 	Appendectomy
A 4-year-old boy ingested Pb shot, which was lodged in his appendix.	<ul style="list-style-type: none"> Prior to surgery (1.5 months after ingestion): 12 	<ul style="list-style-type: none"> Headache 	
Madsen et al. 1988	Range: 4.6–18.2	Not reported	Not reported
Seven patients with Pb shot retained in the appendix.			
McKinney and McKinney 2000	Time after ingestion		
A 5.5-year-old girl ingested several Pb pellets.	<ul style="list-style-type: none"> 13 hours: 57 36 hours: 79 After treatment: <ul style="list-style-type: none"> 14 days: 14.3 6 months: 25 	<ul style="list-style-type: none"> Vomiting and abdominal pain Decreased blood hemoglobin and hematocrit "Mild" speech and language delays noted post-treatment 	<ul style="list-style-type: none"> Whole bowel irrigation Chelation

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Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
McNutt et al. 2001 A 45-year-old male ingested 206 Pb bullets. Medical evaluation occurred 5 days after ingestion. Bullets were spontaneously eliminated over 4–47 days after first medical evaluation.	Time after ingestion: • 5 days: 391 • 10 days: 171 • 25 days: 41 • 6 weeks: 24	• Abdominal pain and gastrointestinal bleeding • Anemia	Chelation started at initial medical visit
McQuirter et al. 2004 Subjects (n=451) 1-year following gunshot wound with retained bullets.	• PbB at time after injury: 1.9 • % with PbB ≥10 (days after injury) ○ 0 days: 2.1 ○ 3 days: 7.6 ○ 18 days: 25.1 ○ 3 months: 38.1 ○ 6 months: 28.5 ○ 12 months: 15.8	Not reported	Not reported
CDC 2004a A 4-year-old boy ingested a Pb medallion.	• 2–3 weeks after ingestion: 123 • After treatment: 57	• Abdominal pain, vomiting, diarrhea • Normocytic anemia, elevated protoporphyrin	• Endoscopy • Chelation
Mowad et al. 1998 An 8-year-old boy ingested several Pb fishing sinkers. Medical assessment was within 1 days of ingestion.	Time after ingestion: • 1 day: 53 • 6 days: 45 (start of chelation) • 1 month: 3	No signs of toxicity observed	• Bowel irrigation • Colonoscopy • Chelation
Rosenberg and Haynes 2019 A 3-year-old ingested Pb pellets.	Time after ingestion: • 7 days: 27 • Post-surgical removal: 14	Not reported	Laparoscopic removal of pellets

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Table C-1. Selected Case Studies of Ingestion of Solid Lead (Pb) Debris or Pb Retained in Gunshot Wounds

Reference and exposure	Blood lead concentration (PbB) (µg/dL)	Effects	Treatment
Rozier and Liebelt 2019 A 2-year-old boy, a 10-year-old boy, and a 16-year old girl ingested Pb pellets.	2-year-old boy, PbB measurement: <ul style="list-style-type: none"> Day 0: 65 5 days post-chelation: 25.2 10-year-old boy, PbB measurement: <ul style="list-style-type: none"> 3 days post-ingestion: 70 7 months post-chelation: 9.5 16-year old girl, PbB measurement: <ul style="list-style-type: none"> 9 days post-ingestion: 53 13 days post-treatment: 3 5 weeks post-treatment: 13 	2-year-old boy: asymptomatic 10-year-old boy: not reported 16-year old girl: <ul style="list-style-type: none"> abdominal pain shortness of breath 	2-year-old boy <ul style="list-style-type: none"> Bowel irrigation Chelation 10-year-old boy <ul style="list-style-type: none"> Bowel irrigation Chelation 16-year old girl <ul style="list-style-type: none"> Bowel irrigation Chelation Colonoscopy
Treble and Thompson 2002 A 2.5-year-old girl ingested Pb pellets.	Time after ingestion <ul style="list-style-type: none"> 1.5 hours: 56 29 hours: 35 94 hours: 35 	No signs of toxicity observed	Laxatives
Zardawi and Siriweera 2013 An 8-year-old boy ingested Pb pellets in game over a 2-year period.	Elevated PbB (17.4–27.4) over 2 years Pellets observed in appendix	Hyperactivity	<ul style="list-style-type: none"> Bowel irrigation Appendectomy

Confounding Factors. There are several uncertainties from case reports on ingestion of Pb debris. Therefore, it is not possible to determine dose, bioavailability, or accurate plasma-time concentration curves. Uncertainties include:

- Baseline PbB data are rarely available. Thus, it is difficult to determine the contribution of ingested Pb debris to measured PbB following ingestion.
- Time from ingestion of Pb debris to first clinical evaluation and PbB assessment is often unknown.
- No quantitative data on the dose of Pb ingested in debris are reported.
- No quantitative data on fecal excretion of ingested Pb are reported.
- Information on the chemical composition of Pb debris often is not reported.
- No information on potential differences in the bioavailability of different types of Pb debris is available

Bioavailability of Pb Debris. No quantitative estimates on the bioavailability of Pb debris in humans are available. Several case reports show increased PbB following ingestion of Pb debris, demonstrating that ingested Pb is absorbed (CDC 2006; Clifton et al. 2002; Durlach et al. 1986; Fergusson et al. 1997; Greensher et al. 1974; Guillard et al. 2006; Hatten et al. 2013; McKinney and McKinney 2000; McNutt et al. 2001; CDC 2004a; Mowad et al. 1998; Treble and Thompson 2002); see Table C-1 for details. However, due to lack of information on ingested dose, quantitative estimates of absorption cannot be determined. No information on bioavailability of Pb debris in animals was identified. Lead debris retained within the body will continue to contribute to elevated PbB until it is removed from the body, either spontaneously or by medical intervention (Banner et al. 2012; Clifton et al. 2002; Durlach et al. 1986; Gerhardsson et al. 2002; Guillard et al. 2006; McQuirter et al. 2004).

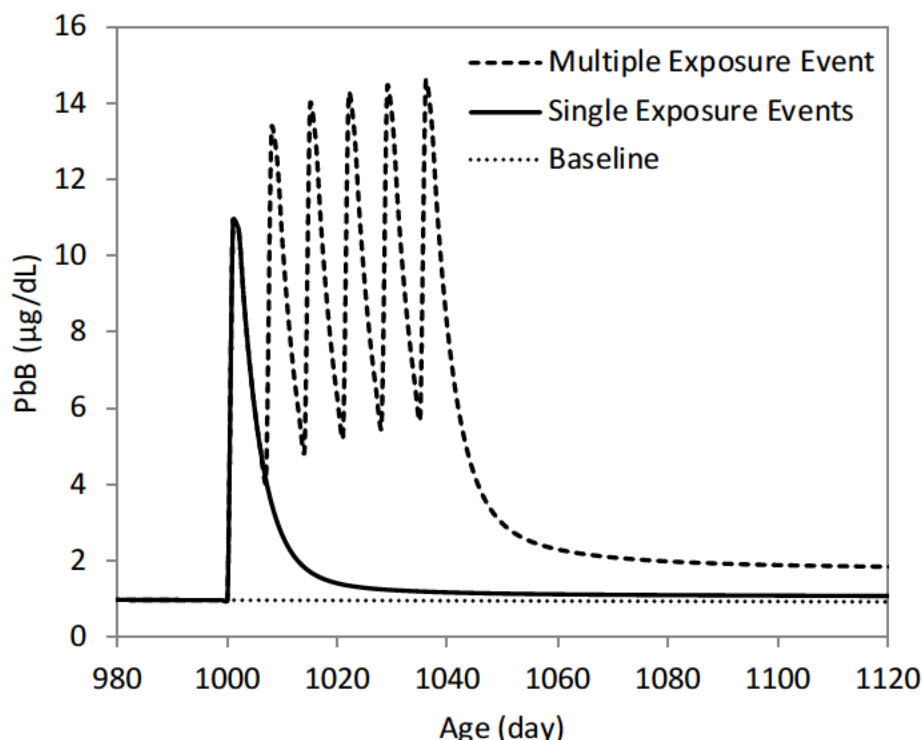
Lead debris must become bioaccessible (i.e., soluble) in the gastrointestinal tract in order for it to be absorbed. It is likely that processes thought to contribute to rendering ingested soil Pb bioaccessible also are important in rendering ingested Pb debris bioaccessible (see Section 3.1.1). IVBA assays that measure extractable Pb have not been evaluated for predicting bioavailability or RBA of ingested Pb debris, although one study found that IVBA measured at gastric pH predicted the relatively high *in vivo* RBA (100%) of firing range soils (Bannon et al. 2009; see Section 3.1.1).

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Although dose-PbB relationships and bioavailability cannot be reliably established from the published case history of Pb debris ingestion, it is possible to use exposure-biokinetics models to reconstruct the time course of PbB expected for a given acute dose of soluble Pb and, from this, estimate the relative bioavailability of Pb from ingested Pb shot that would result in a given peak PbB. This scenario assumes that Pb debris is not retained in the body. The AALM-LG (EPA 2014a) can simulate the internal biokinetics of Pb associated with daily doses of Pb. This model predicts that a child 30 months of age who has a baseline PbB of 1 µg/dL would experience a 10 µg/dL increase in PbB in response to ingestion of approximately 1 mg of soluble Pb (Figure C-1). The peak PbB would occur during the day of ingestion and PbB would return to approximately 120% of baseline in approximately 35 days following the dose. If this prediction is extrapolated to the ingestion of Pb shot or other debris, the 1 mg dose of soluble Pb could occur in association with a dose of 100 mg of debris having an RBA of 1%, or 1 g of debris having an RBA of 0.1% (see Section 3.1.5.4 *EPA All Ages Lead Model [AALM]* for more information). Figure C-1 also shows the predicted PbB pattern for six repeated, weekly events in which the child ingested 1 mg of soluble PbB. This would result in periodic increases in PbB, with the maximum following each exposure event increasing until a pseudo-steady-state PbB was reached at approximately 14.5 µg/dL (13.5 µg/dL above baseline). The PbB would return to approximately 120% of baseline in approximately 570 days after the last exposure event. This longer time to baseline following multiple exposures reflects the accrual of Pb in bone with multiple dosing and the relatively slow transfer of Pb from bone to blood after exposure ceases (see Section 3.1).

Ingestion of soil from firing ranges may also contribute to PbB. A study in juvenile swine of eight soils (sieved to <250 µm) from small arms firing ranges showed a relative bioavailability range of 77–140%, with a mean of 108 % (SD or SE [not specified]: 18%). Soil from this site largely consisted of highly bioavailable Pb carbonate. However, this study did not provide information on bioavailability of Pb debris.

Figure C-1. PbB Predicted from AALM-LG for a 0.9 mg Dose of Soluble Pb Ingested by a Child 30 Months of Age



Retention of Pb Debris in the Appendix. Case reports show that Pb debris can be retained within the appendix (Banner et al. 2012; Cox and Pesola 2005; Durlach et al. 1986; Larsen and Blanton 2000; Lyons and Filston 1994; Madsen et al. 1988; Reddy 1985; Zardawi and Siriweera 2013); see Table C-1 for details. For this to occur, the appendix must be oriented with respect to the cecum in such a way to allow objects to pass through the appendiceal-cecal orifice; approximately 45% of the population have appendices with this orientation. However, approximately 65% of the population have appendices that might hinder foreign body access into the appendiceal lumen due to atypical anatomic position, adhesions, or kinks (Klingler et al. 1998). In addition to orientation of the appendix, the physical size and shape of the debris likely contribute to retention. Although it is not possible to determine the incidence of Pb debris lodged in the gastrointestinal tract or the appendix because not all cases of ingestion of Pb debris are reported in the published literature, approximately 45% of the population is predisposed to retention of Pb debris on orientation of the appendix.

Toxicity of Ingested Pb Debris. Regardless of the source of Pb (e.g., ingested Pb debris, Pb paint, Pb-contaminated soil, occupational exposure), once Pb is absorbed into the body, toxicity will be related to PbB; thus, bioavailability and duration of elevated PbB, rather than the form of Pb ingested, will determine adverse health outcomes. If ingested Pb debris is not retained by the body, toxicity of PbB

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would be consistent with that described for acute Pb toxicity. A summary of peak PbBs and associated toxicity following exposure of ingested Pb debris is shown in Table C-2. Severity of toxicity increases with PbB. At PbB ≤ 47 $\mu\text{g/dL}$, the only adverse health effect observed was a single report of headache at a PbB of 12 $\mu\text{g/dL}$. With increased PbB, effects were observed in several organ systems and severity of effects increased. At a PbB range of 54–146 $\mu\text{g/dL}$, abdominal colic, vomiting, hematological effects, and neurological effects were observed, and at a PbB of 180 $\mu\text{g/dL}$, severe effects (seizure and cerebral edema) leading to death were observed. In most cases, the onset of toxicity occurs within hours or days of ingestion. If PbB remains elevated, either due to inadequate medical intervention or Pb that is retained within the body (i.e., appendix, gastrointestinal tract, etc.) adverse health effects associated with chronically elevated PbB would be expected to occur (see Chapter 2, Health Effects). As reviewed in Chapter 2, PbBs ≤ 10 $\mu\text{g/dL}$ are associated with adverse health effects to numerous organ systems, including developmental and neurological effects, with severity exhibiting dose-dependence. Given the many factors that can affect development of Pb-induced toxicity, case reports of individuals cannot provide generalizations of exposure-response relationships.

Table C-2. Peak Blood Lead Concentration (PbB) and Acute Toxicity Associated with Ingestion of Lead (Pb) Debris

Peak PbB ($\mu\text{g/dL}$) ^a	Effects associated with Pb exposure	References
12–16	No effects observed	Fergusson et al. 1997
	Headache	Lyons and Filston 1994
40.5–47	No effects observed	Clifton et al. 2002; Hatten et al. 2013
54–61	No effects observed	Mowad et al. 1998; Treble and Thompson 2002
	Abdominal colic Hematological effects ^b	Banner et al. 2012
79	Abdominal colic and vomiting	McKinney and McKinney 2000
	Hematological effects ^c	
	Neurological effects ^d	
123	Abdominal colic, vomiting, diarrhea Hematological effects ^e	CDC 2004a
146	Vomiting	Hatten et al. 2013
	Neurological signs ^f	
180	Vomiting	CDC 2006
	Seizures	
	Cerebral edema	
	Death	

Table C-2. Peak Blood Lead Concentration (PbB) and Acute Toxicity Associated with Ingestion of Lead (Pb) Debris

Peak PbB (µg/dL) ^a	Effects associated with Pb exposure	References
391	Abdominal colic, gastrointestinal bleeding Anemia	McNutt et al. 2001

^aPeak blood Pb reported.^bElevated free erythrocyte protoporphyrin or microcytic anemia and increased blood zinc protoporphyrin.^cDecreased blood hemoglobin and hematocrit.^d"Mild" speech and language delays.^eNormocytic anemia, elevated protoporphyrin^fDecreased activity level and hyperactive patellar and brachioradialis reflexes.

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APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2	Children and Other Populations that are Unusually Susceptible
Section 3.3	Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: <http://www.atsdr.cdc.gov>

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see <https://www.atsdr.cdc.gov/csem/csem.html>).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see <https://www.atsdr.cdc.gov/MHMI/index.asp>). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see <https://www.atsdr.cdc.gov/toxfaqs/Index.asp>).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: <https://www.cdc.gov/nceh/>.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/niosh/>.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: <https://www.niehs.nih.gov/>.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: <http://www.acoem.org/>.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: <http://www.acmt.net>.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at <http://pehsu.net/findhelp.html>.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: <http://www.aapcc.org/>.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤ 14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥ 365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m³ or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥ 1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD _x	dose that produces a X% change in response rate of an adverse effect
BMDL _x	95% lower confidence limit on the BMD _x
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

APPENDIX F

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ -glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kgg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

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NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

APPENDIX F

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q ₁ [*]	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

TOXICOLOGICAL PROFILE FOR SELENIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2003

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for selenium, Draft for Public Comment was released in September, 2001. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.


The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.


Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	How Can (Chemical X) Affect Children?
Section 1.7	How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7	Children's Susceptibility
Section 6.6	Exposures of Children

Other Sections of Interest:

Section 3.8	Biomarkers of Exposure and Effect
Section 3.11	Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 **Fax:** (404) 498-0093

E-mail: atsdric@cdc.gov

Internet: <http://www.atsdr.cdc.gov>

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for selenium. The panel consisted of the following members:

1. Orville Levander, Ph.D., Silver Springs, Maryland
2. Gregory Möller, Ph.D., Associate Professor of Environmental Chemistry and Toxicology, Moscow, Indiana
3. Raghubir Sharma, Ph.D., D.V.M., Professor of Physiology and Pharmacology, Athens, Georgia

These experts collectively have knowledge of selenium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about selenium and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Selenium has been found in at least 508 of the 1,623 current or former NPL sites. However, the total number of NPL sites evaluated for selenium is not known. As more sites are evaluated, the sites at which selenium is found may increase. This information is important because exposure to selenium at high levels may harm you and because these sites may be sources of exposure. A minimum dietary level of selenium is required for good health.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to selenium, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it/them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS SELENIUM?

Selenium is a naturally occurring, solid substance that is widely but unevenly distributed in the earth's crust. It is also commonly found in rocks and soil. Selenium, in its pure form of metallic gray to black crystals, is often referred to as elemental selenium or selenium dust. Elemental selenium is commercially produced, primarily as a by-product of copper refining. Selenium is not often found in the environment in its elemental form, but is usually combined with other

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substances. Much of the selenium in rocks is combined with sulfide minerals or with silver, copper, lead, and nickel minerals. Selenium also combines with oxygen to form several substances that are white or colorless crystals. Some selenium compounds are gases. Selenium and its compounds are used in some photographic devices, gun bluing (a liquid solution used to clean the metal parts of a gun), plastics, paints, anti-dandruff shampoos, vitamin and mineral supplements, fungicides, and certain types of glass. For example, selenium sulfide is used in anti-dandruff shampoos by the common trade name Selsun Blue. Selenium is also used to prepare drugs and as a nutritional feed supplement for poultry and livestock. More information on the chemical and physical properties, production, and uses of selenium are found in Chapters 4 and 5.

1.2 WHAT HAPPENS TO SELENIUM WHEN IT ENTERS THE ENVIRONMENT?

Selenium occurs naturally in the environment. As an element, selenium cannot be created or destroyed, although selenium can change forms in the environment. Weathering of rocks and soils may result in low levels of selenium in water, which may be taken up by plants. Weathering also releases selenium into the air on fine dust-like particles. Volcanic eruptions may release selenium in air. Selenium commonly enters the air from burning coal or oil. Selenium that may be present in fossil fuels combines with oxygen when burned, which may then react with water to form soluble selenium compounds. Airborne particles of selenium, such as in ash, can settle on soil or surface water. Disposal of selenium in commercial products and waste could also increase the amount of selenium in soil. The forms and fate of selenium in soil depend largely on the acidity of the surroundings and its interaction with oxygen. In the absence of oxygen when the soil is acidic, the amount of selenium that can enter plants and organisms should be low. Elemental selenium that cannot dissolve in water and other insoluble forms of selenium are less mobile and will usually remain in the soil, posing smaller risk of exposure. Selenium compounds that can dissolve in water are sometimes very mobile. Thus, there is an increased chance of exposure to these compounds. Selenium may enter surface water in irrigation drainage waters. Some evidence indicates that selenium can be taken up in tissues of aquatic organisms and possibly increase in concentration as the selenium is passed up through the food chain. Selenium concentrations in aquatic organisms have been a problem as a result of

irrigation runoff in some dry areas of the United States. Chapter 6 contains more information on what happens to selenium in the environment.

1.3 HOW MIGHT I BE EXPOSED TO SELENIUM?

People are exposed to low levels of selenium daily through food, water, and air. Selenium is also an essential nutrient for humans and animals. However, selenium can be harmful when regularly taken in amounts higher than those needed for good health. People receive the majority of their daily intake of selenium from eating food, and to a lesser extent, from water intake. Estimates of the average intake of selenium from food for the U.S. population range from 71 to 152 millionths of a gram of selenium per person per day. Low levels of selenium can also be found in drinking water. Selenium levels are less than 10 parts of selenium in a billion parts of water (10 ppb) in 99.5% of drinking water sources tested. People may be exposed to higher-than-normal levels of selenium at hazardous waste sites by swallowing soil or water, or by breathing dust. In some parts of the United States, especially in the western states, some soils naturally have higher levels of selenium compounds. Some plants can build up selenium to levels that harm livestock feeding on them. In these areas, people could be exposed to too much selenium if they eat a lot of locally grown grains and vegetables or animal products that have built up high levels of selenium. People may also be exposed to selenium from industrial sources. Humans are normally not exposed to large amounts of selenium in the air, unless selenium dust or volatile selenium compounds are formed in their workplace. Occupations in which humans may be exposed to selenium in the air are the metal industries, selenium-recovery processes, paint manufacturing, and special trades. Chapter 6 contains more information on how people can be exposed to selenium.

1.4 HOW CAN SELENIUM ENTER AND LEAVE MY BODY?

Selenium from the environment mainly enters the body when people eat food containing selenium. The human body easily absorbs the organic selenium compounds (for example, selenoamino acids) when eaten, and makes them available where needed in the body. The

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selenium in drinking water is usually in the form of inorganic sodium selenate and sodium selenite; these forms of selenium are also easily absorbed from the digestive tract. The human body can change these inorganic selenium compounds into forms that it can use. Selenium in the air may also enter your body when you breathe it.

Hazardous waste sites at which selenium is present could represent a major source of exposure. The way that selenium can enter the body from a particular site depends on such factors as whether vegetables are grown in soil in which selenium from the site has been deposited, whether water at the site contains selenium and is able to flow into drinking water supplies, and whether selenium dust blows into the air. As mentioned earlier, specific conditions at a site can greatly influence which selenium compounds form and whether they can move in the environment to places where people might be exposed. Therefore, it is important to know that the presence of selenium at a site does not necessarily mean that people are being exposed to it. Specific tests of locally grown food, drinking water, and air must be done to find out whether exposure is occurring. You should also be aware that selenium compounds, including those used in some medicated dandruff shampoos, are not easily absorbed through the skin.

Most of the selenium that enters the body quickly leaves the body, usually within 24 hours. Beyond what the body needs, selenium leaves mainly in the urine, but also in feces and breath. Selenium in the urine increases as the amount of the exposure goes up. Selenium can build up in the human body, however, if exposure levels are very high or if exposure occurs over a long time. The amount that builds up in the body depends on the chemical form of the selenium. It builds up mostly in the liver and kidneys but also in the blood, lungs, heart, and testes. Selenium can build up in the nails and in hair, depending on time and amount of exposure. Chapter 3 contains more information on how selenium enters and leaves the human body.

1.5 HOW CAN SELENIUM AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

1. PUBLIC HEALTH STATEMENT

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

The general public rarely breathes high levels of selenium, although some people may be exposed to selenium dust and selenium compounds in workplace air. Dizziness, fatigue, and irritation of mucous membranes have been reported in people exposed to selenium in workplace air at concentrations higher than legal levels. In extreme cases, collection of fluid in the lungs (pulmonary edema) and severe bronchitis have been reported. The exact exposure levels at which these effects might occur are not known, but they become more likely with increasing amounts of selenium and with increasing frequency of exposure.

The normal intake of selenium by eating food is enough to meet the Recommended Daily Allowance (RDA) for this essential nutrient. However, as discussed in Chapters 2 and 3 of this profile, selenium compounds can be harmful at daily dietary levels that are higher than needed. The seriousness of the effects of excess selenium depends on how much selenium is eaten and how often. Intentional or accidental swallowing of a large amount of sodium selenate or sodium selenite (for example, a very large quantity of selenium supplement pills) could be life-threatening without immediate medical treatment. Even if mildly excessive amounts of selenium are eaten over long periods, brittle hair and deformed nails can develop. In extreme cases, people may lose feeling and control in arms and legs. These health effects, called selenosis, were seen in several villages in China where people were exposed to foods high in selenium for months to years. No human populations in the United States have been reported with long-term selenium poisoning, including populations in the western part of the country where selenium levels are naturally high in the soil. Because most people in the United States eat foods produced in many different areas, overexposure to selenium in food is unlikely to occur.

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In some regions of China where soil levels of selenium are very low, not eating enough selenium has resulted in health effects. Selenium is used by the body in antioxidant enzymes that protect against damage to tissues done by oxygen, and in an enzyme that affects growth and metabolism. Not eating enough selenium can cause heart problems and muscle pain. Muscle pain has also been noted in people fed intravenously for a long time with solutions that did not contain selenium. Babies born early may be more sensitive to not having enough selenium, and this may contribute to lung effects. In the United States, selenium in food is sufficient to meet the RDA and prevent harmful effects from not enough selenium.

Upon contact with human skin, industrial selenium compounds have been reported to cause rashes, redness, heat, swelling, and pain. Brief, acute exposure of the eyes to selenium dioxide as a dust or fume in workplace air may result in burning, irritation, and tearing. However, only people who work in industries that process or use selenium or selenium compounds are likely to come into contact with levels high enough to cause eye irritation.

Studies of laboratory animals and people show that most selenium compounds probably do not cause cancer. In fact, some studies of cancer in humans suggest that lower-than-normal selenium levels in the diet might increase the risk of cancer. Other studies suggest that dietary levels of selenium that are higher than normal might reduce the risk of cancer in humans. However, taking selenium so that your daily amount is greater than that required might just increase your risk of selenium poisoning.

Based on studies done until 1987, the International Agency for Research on Cancer (IARC) determined that selenium and selenium compounds could not be classified as to their ability to cause cancer in humans. However, since then, the EPA has determined that one specific form of selenium, called selenium sulfide, is a probable human carcinogen. Selenium sulfide is the only selenium compound shown to cause cancer in animals. Rats and mice that were fed selenium sulfide daily at very high levels developed cancer. Selenium sulfide is not present in foods, and it is a very different chemical from the organic and inorganic selenium compounds found in foods and in the environment. Also, if introduced into the environment, selenium sulfide does not dissolve readily in water and would probably bind tightly to the soil, further reducing any

chance of exposure. Because selenium sulfide is not absorbed through the skin, the use of anti-dandruff shampoos containing selenium sulfide is generally considered safe.

Very high amounts of selenium have caused decreased sperm counts, increased abnormal sperm, changes in the female reproductive cycle in rats, and changes in the menstrual cycle in monkeys. The relevance of the reproductive effects of selenium exposure in animals studied to potential reproductive effects in humans is not known. Selenium compounds have not been shown to cause birth defects in humans or in other mammals.

Chapter 3 contains more information on the health effects of selenium and selenium compounds in humans and animals.

1.6 HOW CAN SELENIUM AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children living near selenium waste sites or coal burning plants are likely to be exposed to higher environmental levels of selenium through breathing, touching soil, and eating contaminated soil. Children living in areas of China with high selenium in the soil had higher levels of selenium in the blood than adults from that area. Very few studies have looked at how selenium can affect the health of children. Children need small amounts of selenium for normal growth and development. Children will probably show the same sort of health effects from selenium exposure as adults, but some studies suggest that they may be less susceptible to health effects of selenium than adults.

We do not know if exposure to selenium could result in birth defects in people. Selenium compounds have not been shown to cause birth defects in humans or in other mammals. We have no information to suggest that there are any differences between children and adults in where selenium is found in the body or in how fast it enters or leaves the body. Studies in laboratory animals have shown that selenium crosses the placenta and enters the fetus. Studies in

humans show that infants are supplied with selenium through breast milk, and therefore, women who were exposed to selenium by living near a waste site might transfer selenium to their babies. However, babies in areas of China with high selenium in the soil did not show any signs of health effects due to selenium, even though some of their parents did.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO SELENIUM?

If your doctor finds that you have been exposed to significant amounts of selenium, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Since selenium occurs naturally in the environment, we cannot avoid exposure to it. Certain dietary supplements and anti-dandruff shampoos contain selenium in high levels. You should not exceed the recommended dosages when using these products.

Children living near selenium waste sites or coal burning plants are likely to be exposed to higher environmental levels of selenium through breathing, touching soil, and eating contaminated soil. Some children eat a lot of dirt. You should discourage your children from eating dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or from other hand-to-mouth activity.

The primary route of human exposure to selenium is through eating food. People who irrigate their home gardens with groundwater containing high levels of selenium may grow and eat plants that contain high levels of selenium because this element is taken up in some plants. Fishermen and hunters of waterfowl who regularly eat fish and game from waterways with high selenium content may also consume above average levels of selenium. To reduce your family's exposure to selenium, obey any wildlife advisories issued by your state. Information on fish and wildlife advisories in your state is available from your state public health or natural resources department.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SELENIUM?

Selenium can be measured in the blood, urine, and fingernails or toenails of exposed individuals. However, since selenium is an essential nutrient normally present in foods, low levels of selenium are normally found in body tissues and urine. Tests for selenium are most useful for people who have recently been exposed to high levels. Samples of blood, urine, or nails can be properly collected in a physician's office and sent to a laboratory that has the special equipment needed to measure selenium. Urine can be used to determine short-term exposure. Because red blood cells last about 120 days before they are replaced by newly made red blood cells, the presence of selenium in red blood cells can show whether a person was exposed to selenium during the 120 days before testing, but not if exposed more than 120 days before testing. Toenail clippings can be used to determine longer-term exposure.

Many methods are available to measure selenium levels in human tissue and the environment. However, none of the methods that are routinely available can measure or detect each selenium compound in one test, and better tests that measure lower levels of different selenium compounds are needed. Also, these tests cannot determine the exact levels of selenium you may have been exposed to or predict whether health effects will occur, even though very high amounts of selenium in blood are clearly related to selenosis. Some human as well as animal studies suggest that when people are exposed over a long period to higher-than-normal amounts of selenium, their bodies adjust to the higher amounts. Chapter 3 contains more information on studies that have measured selenium in blood and other human tissues.

The length of time that selenium stays in the body after exposure stops depends on the form of selenium to which the person was exposed. Thus, it is difficult to predict how useful a test will be if some time has gone by since exposure stopped. Chapter 7 contains more information on the methods available to measure selenium in human tissues and in the environment.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health.

Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for selenium include the following:

The EPA Office of Drinking Water regulates the amount of selenium allowed in drinking water. Public water supplies are not allowed to exceed 50 ppb total selenium.

The FDA regulations allow a level of 50 ppb of selenium in bottled water. OSHA is responsible for setting regulations on selenium levels allowable in the workplace. The exposure limit for selenium compounds in the air for an 8-hour period is 0.2 mg selenium/m³. Chapter 8 contains other regulations and guidelines for selenium.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: <http://www.ntis.gov/>

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SELENIUM IN THE UNITED STATES

Selenium is an essential micronutrient for humans and animals that is found ubiquitously in the environment, being released from both natural and anthropogenic sources. The principal release of selenium into the environment from anthropogenic sources is from coal combustion. Natural sources of selenium include the weathering of selenium-containing rocks and soils, and volcanic eruptions. Selenium is found in most rocks and soils, and naturally occurs at low concentrations in surface waters and groundwaters of the United States. Accumulation of selenium in agricultural drainage waters has been documented in basins in the western United States, particularly in California. Ambient background concentrations of selenium in the air are very low, generally in the nanogram per cubic meter (ng/m³) range.

Exposure of the general population to selenium is primarily by ingestion of its organic and inorganic forms, both of which occur naturally in the diet. The greatest portion of dietary intake occurs from organic forms of selenium, mainly the amino acids selenomethionine and selenocysteine, in grains, cereals, and forage crops. The main inorganic sources of selenium in the diet are selenate and selenite, which are less absorbed than the organic forms. Other exposure pathways for selenium, which are of lesser importance, are water and air. Various estimates of the selenium intake for Americans have ranged from 0.071 to 0.152 mg selenium/day (approximately 1–2 µg/kg/day in adults). Some people living in areas with high soil concentrations of selenium (as in areas of the western United States) might have higher exposure because of the natural selenium levels found locally, particularly if they consume crops primarily grown in that area. Metal industry workers, health service professionals, mechanics, and painters may be exposed to higher levels of selenium than the general population or workers employed in other trades.

2.2 SUMMARY OF HEALTH EFFECTS

As an essential trace element in humans and animals, selenium is a biologically active part of a number of important proteins, particularly enzymes involved in antioxidant defense mechanisms (e.g., glutathione peroxidases), thyroid hormone metabolism (e.g., deiodinase enzymes), and redox control of intracellular

2. RELEVANCE TO PUBLIC HEALTH

reactions (e.g., thioredoxin reductase). Depending upon the level of intake, selenium can have nutritional or possibly toxic effects. Most people in the United States are unlikely to suffer from selenium deficiency. Although excessive intake of selenium can cause adverse health effects, these are generally observed at doses more than 5 times greater than the Recommended Dietary Allowance (RDA).

The current RDA for selenium, established by the Food and Nutrition Board of the National Research Council (National Academy of Sciences), is 55 µg/day for male and female adults (approximately 0.8 µg/kg/day). This recommendation represents a decrease from the previous RDA of 70 µg/day for males; 55 µg/day was already the RDA for females. The current NAS Tolerable Upper Intake Level (UL) for selenium is 400 µg/day for adults (approximately 5.7 µg/kg/day). At the time that the RDA was in the process of being reevaluated (i.e., late 1990s), selenium was found to have entered the environment from old mining operations in some northwestern U.S. locations. This resulted in public concern about the potential effects of selenium on livestock grazing in the vicinity, and ultimately possible effects in humans consuming food products from plants and animals raised in those areas. The combination of the increased concern regarding selenium toxicity and the reduction in the selenium RDA indicated to ATSDR that an Agency reevaluation of selenium from a toxicological perspective is warranted; the previous version of the ATSDR Toxicological Profile for Selenium was published in 1996.

Although selenium deficiency is not a health issue in the United States, it has been associated with two endemic diseases found in selenium-poor regions of China: a cardiovascular condition known as Keshan Disease and an osteoarthropathy called Kashin-Beck Disease. Keshan Disease is a cardiomyopathy characterized by cardiac enlargement, abnormal ECG patterns, cardiogenic shock, and congestive heart failure, with multifocal necrosis of the myocardium. The disease is reported to occur primarily in children and women of child-bearing age and has been successfully treated by selenium supplementation; however, a low incidence of cases persisting after selenium supplementation suggests that there may be other contributing factors. The evidence for the involvement of selenium in Kashin-Beck disease is less clear than for its involvement in Keshan disease. Kashin-Beck Disease is characterized by atrophy, degeneration, and necrosis of cartilage tissue, and occurs primarily in children between the ages of 5 and 13 years; it also has been successfully treated with selenium supplements. Chronically ill people and older people have been shown to have lower organ concentrations of selenium than healthy individuals, but it is not clear if this is a cause or consequence of aging or illness.

Relatively little information is available on health effects of elevated inhalation levels of selenium. The primary target organ in humans and laboratory animals in cases of acute, high-level inhalation exposure to

selenium dusts or fumes is the lung, with cardiovascular, hepatic, nervous, and renal involvement as well. Lesser effects are observed in other organs/organ systems. Workers acutely exposed to high concentrations of elemental selenium dust have reported stomach pain and headaches, whereas workers briefly exposed to high levels of selenium dioxide dust experienced respiratory symptoms such as pulmonary edema, bronchial spasms, symptoms of asphyxiation and persistent bronchitis, elevated pulse rates, lowered blood pressure, vomiting, nausea, and irritability. No information is available on health effects in humans or laboratory animals from intermediate-duration (up to 1 year) inhalation exposure to selenium or selenium compounds. Regarding chronic inhalation exposure, several occupational studies describe respiratory effects such as irritation of the nose, respiratory tract, and lungs, bronchial spasms, and coughing following exposure to selenium dioxide or elemental selenium as dust. Respiratory symptoms similar to those reported for occupationally-exposed humans have been seen in animals inhaling high doses of elemental selenium fumes or dust, and studies of animals with acute inhalation exposure to hydrogen selenide or elemental selenium fumes or dust have reported hepatocellular degeneration and atrophy of the liver.

Acute oral exposure to extremely high levels of selenium (e.g., several thousand times more than normal daily intake) produces nausea, vomiting, and diarrhea in both humans and laboratory animals. Acute oral exposure of humans to selenium has occasionally caused cardiovascular symptoms, such as tachycardia, but no electrocardiographic abnormalities were found in individuals from a human population chronically exposed to selenium. In laboratory animals, acute- and intermediate-duration oral exposure to very large amounts of selenium (approximately 100 times normal human intake) has produced myocardial degeneration in laboratory animals.

Chronic oral intake of very high levels of selenium (10–20 times more than normal) can produce selenosis in humans, the major effects of which are dermal and neurological. As shown by affected populations in China, chronic dietary exposure to these excess levels of selenium has caused diseased nails and skin and hair loss, as well neurological problems, including unsteady gait and paralysis. Additional information on selenosis is summarized in the following subsection of this chapter. In contrast, studies of people living in areas of naturally occurring high selenium concentrations in the United States have not revealed adverse health effects in those populations. This difference may result from a lower (~2-fold) selenium exposure in the U.S. population compared to the Chinese population, as well as a better balanced, higher protein diet in the United States, which could lead to reduced toxicity of selenium through interactions with dietary components.

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Intermediate and chronic oral exposure of livestock to high levels of dietary selenium compounds also produces dermal and neurological effects. Studies in rats and other laboratory animals with high selenium tissue concentrations demonstrate that many organ systems retain selenium and are affected. The primary adverse effects in laboratory animals exposed to inorganic selenium salts or to selenium-containing amino acids are cardiovascular, gastrointestinal, hematological, hepatic, dermal, immunological, neurological, and reproductive, although doses causing these effects are generally at least 5 times higher than normal daily selenium intake. A condition (syndrome) referred to as “blind staggers” has been repeatedly observed in cattle feeding off vegetation in areas with high selenium content in the soil. However, the neurological effects have not been replicated in experimentally-exposed cattle receiving doses of selenium sufficient to induce hoof lesions, and thus, the neurological signs associated with “blind staggers” may be due to other compounds found within this vegetation.

Some evidence for effects on the endocrine system has also been found following long-term oral exposure to elevated levels of dietary selenium in humans and rats. In humans, blood levels of thyroid T₃ hormone (triiodothyronine) decreased in response to increased dietary selenium for durations of 3 months and longer at intakes several times higher than normal intake, although the hormone levels remained within the normal range. In rats, type-I-deiodinase activity decreased in response to increased exposure to selenium for several months, but the levels of thyroid hormones in these animals did not show a consistent pattern.

Studies of Chinese populations and laboratory animals exposed to high levels of organic and/or inorganic selenium compounds have not found evidence of selective teratogenic effects in mammals.

There is no evidence to support a causal association between selenium compounds and cancer in humans. In fact, some epidemiological and experimental evidence suggests that selenium exposure under certain conditions may contribute to a reduction in cancer risk. The chemopreventive potential of supplemental selenium is currently under research. Selenium sulfide and ethyl selenac are the only selenium compounds that have been shown to be carcinogenic upon oral administration in rodents; however, significant exposure of humans to these chemical forms of selenium is extremely unlikely.

Additional information on main health effects of selenium in humans and animals is summarized below and detailed in Chapter 3.

Selenosis. Following chronic oral exposure to excessive amounts of the organic selenium compounds in food, the two principal clinical conditions observed in humans are dermal and neurological effects, as described most completely in the epidemiological study of endemic selenosis in the People's Republic of China. The dermal manifestations of selenosis include loss of hair, deformation and loss of nails, and discoloration and excessive decay of teeth, while neurological effects include numbness, paralysis, and occasional hemiplegia. The average dietary intake of selenium associated with selenosis in these people has been estimated to be 1,270 µg/day (~0.02 mg/kg/day, or 10–20 times higher than normal daily intake).

Loss of hair and malformation of hooves in pigs, horses, and cattle, and poliomyelomalacia in pigs have been reported to occur following long-term exposure to excessive amounts (more than 30 times the normal dietary amount of selenium) of the organic selenium compounds found in seleniferous plants. Histologically, swine with selenium-induced neurological signs exhibit bilateral macroscopic lesions of the ventral horn of the spinal cord. The selenium in the selenium-accumulating plant *Astragalus bisulcatus* appears to be a more potent neurotoxicant than D,L-selenomethionine or selenate. The form of selenium in *A. bisulcatus* is unknown, although it is apparently nonprotein. Myocardial degeneration has been experimentally produced in cattle, sheep, and swine (as well as in laboratory mammals) by acute and longer-term exposures to inorganic salts of selenium, but it is unclear whether seleniferous grains or forages, or other natural sources of selenium, cause the same cardiomyopathy.

The neurological signs and histopathology observed in livestock following oral exposure to excess selenium compounds have not been recorded in laboratory animals. This suggests that (1) small laboratory mammals might not be appropriate models for selenium toxicity in humans due to toxicokinetic differences (e.g., laboratory animals absorb selenium compounds to a lesser extent, or metabolize and/or excrete selenium compounds more quickly), (2) some as yet unidentified organic form of selenium contributes to the neurological manifestations of chronic selenosis in humans and in livestock, (3) unrecognized confounding factors, such as other plant toxins, have contributed to the neurological syndrome associated with chronic selenosis in field studies of humans and livestock, and/or (4) species differences in interactions between selenium and other nutrients or xenobiotics, such as vitamin E and methionine, which have been found to be antagonistic to selenium toxicity

Endocrine Effects. Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones, and has a physiological role in the

control of thyroid hormone levels. Significant decreases in serum T₃ hormone levels have been observed in humans that were environmentally or experimentally exposed to elevated dietary levels of selenium (several times higher than normal). However, the T₃ hormone levels observed in these studies were still within the normal human range, so the biological impact of this change is unclear. The effect of increased dietary selenium on other thyroid hormones is also uncertain. Intermediate-duration studies in rats show a decrease in type-I-deiodinase activity in response to elevated selenium; however, the levels of thyroid hormones in these animals did not show any consistent changes.

Reduced growth rate of young animals and weight loss in older animals are two of the most common effects in experimental animals following long-term oral intake of excessive levels of inorganic and organic compounds of selenium. It is quite possible that selenium-induced reduction in growth has a thyroid or other endocrine component. For example, selenite treatment of young rats decreased somatomedin C levels, although somatomedin C was not a sensitive index of elevated selenium exposure in humans from a high-selenium area of South Dakota, and growth hormone secretion in response to the growth hormone releasing factor was also reduced in selenium-treated rats. The primary endocrine target of selenium leading to decreased growth has yet to be elucidated. Pancreatic toxicity has been observed following excess selenium exposure. Cytoplasmic flocculation was observed in lambs treated with a single oral dose of selenite, and pancreatic damage, which was not further described, was noted in rats following chronic oral treatment with selenate or selenite. Pancreatic toxicity associated with excessive selenium exposure is likely related to the unique ability of that organ to accumulate the element.

Reproductive Effects. In humans, no correlation has been found between selenium levels in seminal fluid and sperm count or mobility. No significant increase in spontaneous abortions was reported among women chronically exposed to drinking water containing increased selenium, but the concentration was not considered to be unusually high. In animals, oral exposure to high doses of sodium selenate or selenite (at least 8 times greater than those normally supplied by an adequate diet) caused increased numbers of abnormal sperm, as well as testicular hypertrophy, degeneration, and atrophy in male rats, and affected the estrous cycle in female rats and mice. The animals that showed these effects were not mated, so it is not clear if fertility was affected. Oral treatment with L-selenomethionine similarly caused disturbances in the menstrual cycle (anovulation, short luteal and follicular phases) in monkeys. Selenium deficiency has also been reported to cause decreased sperm production and motility in rats. The relevance of the reproductive effects of high and low levels of selenium in laboratory animals to potential reproductive effects in humans is not known.

Hepatic Effects. Liver effects have not been reported for humans exposed to excessive amounts of selenium. No significant abnormalities were found in blood levels of liver enzymes in people living in high selenium areas, or in liver morphology (ultrasonographic examination) of individuals suffering from severe symptoms of selenosis. In experimental animals and livestock, however, the liver has been shown to be affected following inhalation or oral exposure to different kinds of selenium compounds. Hepatocellular degeneration occurred in guinea pigs following short-term inhalation exposure to excessive levels (hundreds of times higher than normal) of elemental selenium dust (8 mg/m^3) or hydrogen selenide (33 mg/m^3). Cirrhosis, hepatocellular degeneration, and changes in liver enzyme levels in serum have been reported for rats, pigs, and mice orally exposed to selenite, selenate, or organic selenium. The oral doses of selenium producing the various adverse liver effects were approximately 10 times the amount normally found in an adequate diet. Excessive dietary exposure to selenium sulfide (several thousands of times higher than normal selenium intake) produced frank hepatotoxicity in rats, but not in mice. Although the liver appears to be the primary target organ for the oral toxicity of selenium in experimental animals following intermediate and chronic exposure, liver cirrhosis or dysfunction has not been a notable component of the clinical manifestations of chronic selenosis in humans. The lack of evidence of liver damage in humans due to selenosis, despite all of the animal data to the contrary, suggests a problem with the animal models of the disease.

Renal Effects. No reports of renal effects in humans were located. In animals, mild kidney effects have been observed following oral exposure to selenium at levels several hundred times higher than normal human intake. These effects include hydropic degeneration in sheep following a single dose of 5 mg Se/kg/day as sodium selenite. Rats appear to be more sensitive than mice to renal effects of repeated oral exposures to selenium compounds. A dose-related increase in renal papilla degeneration, described as mild to minimal, was observed in rats at very high levels of selenate or selenite (0.5 mg Se/kg/day , several hundreds of times higher than normal human intake) in the drinking water for 13 weeks, although increased kidney weight was the only renal effect in similarly exposed mice. Mice that were given excessive daily doses of selenium sulfide by gavage (464 mg Se/kg/day for 13 weeks), however, developed interstitial nephritis.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

No MRLs were derived for inhalation exposure to selenium because of insufficient quantitative data concerning both human and animal exposures. Data on the health effects of inhaled selenium in humans are available from studies of occupationally exposed workers (Clinton 1947; Glover 1970; Holness et al. 1989; Kinnigkeit 1962; Wilson 1962). These studies suggest that the respiratory system is the most sensitive end point for inhaled selenium dust, but they do not provide quantitative measurements of exposure levels and are frequently confounded by concurrent exposures to other chemicals. Laboratory animal studies support the respiratory system as the main target of selenium inhalation toxicity (Dudley and Miller 1941; Hall et al. 1951), but the available data are for acute exposures to high concentrations of selenium that also produced serious health effects, including death.

Oral MRLs

No MRLs were derived for acute or intermediate oral exposure to selenium because of insufficient information regarding adverse health effect levels in humans and experimental animals. For acute exposure, no quantitative data are available from studies of humans. Some acute oral animal studies identify lowest-observed-adverse-effect levels (LOAELs) for organ weight changes, behavioral changes, and reduced body weight, but these occur at doses similar to those producing serious LOAELs for paralysis and developmental effects in other mammalian studies.

Information on health effects of intermediate-duration (15–365 days) oral exposure to selenium in humans is mainly available from a 120-day experimental study of men who were exposed to a controlled diet of foods naturally low or naturally high in selenium (Hawkes and Turek 2001; Hawkes et al. 2001). Eleven subjects were fed diets providing selenium intake levels of 0.6 µg/kg/day for 21 days (baseline period), followed by 0.2 µg/kg/day (6 subjects) or 4 µg/kg/day (5 subjects) for the subsequent 99 days. This was more a nutritional study than a toxicological study, as indicated by selenium intake levels that bracketed the current RDA (~0.8 µg Se/kg/day) and were well below the tolerable upper limit (~5.7 µg Se/kg/day) recommended by the Food and Nutrition Board (NAS 2000). Comprehensive evaluations were performed that included serum levels of thyroid hormones (T₃ and TSH) and reproductive hormones (testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone), sperm quality indices (number and concentration, motility, forward progression and velocity, and morphology), and immunological end points (including serum immunoglobulin levels, lymphocyte counts

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and phenotypes, natural-killer cell activity, proliferative response of lymphocytes to mitogenic stimulation, delayed-type hypersensitivity skin responses to recall antigens, and antibody responses to diphtheria-tetanus and influenza vaccines). Effects were essentially limited to subclinical changes in thyroid hormones and sperm motility, which are not considered to be toxicologically meaningful. Serum T₃ concentrations decreased in the high selenium group and increased in the low selenium group, but all values apparently remained within the normal human range. Serum TSH concentrations increased in the high-selenium group with no change in the low-selenium group, but values also remained in the normal range. Sperm motility was slightly lower than the baseline value in the high selenium group at study termination. The decrease in sperm motility cannot be clearly attributed to selenium because the effect was not consistent over the duration of exposure, and is unlikely to be adverse because it is at the low end of the normal range and was not accompanied by any changes in other indices of sperm movement (progression or forward velocity) or sperm numbers or morphology.

Effects in intermediate-duration studies in experimental animals include reductions in liver enzyme activities, changes in liver and body weights, and histological changes in the liver and kidney, but the relevance of these effects to selenium toxicity in humans is questionable. For example, humans with selenosis did not display any changes in serum levels of liver enzymes or morphological damage to the liver, as shown by ultrasonographic examination (Yang et al. 1989a). Further, the liver and kidney effects in animal studies occurred at doses (≥ 0.2 mg/kg/day) that were considerably higher than the 4 $\mu\text{g/kg/day}$ intake level that caused the subclinical thyroid hormone and sperm motility alterations in humans (Hawkes and Turek 2001; Hawkes et al. 2001). Although the human experimental study identifies a no-observed-adverse-effect level (NOAEL) of 4 $\mu\text{g/kg/day}$ for sensitive endocrine and male reproductive end points, it is an inappropriate basis for derivation of an intermediate oral MRL. In particular, because this is a free-standing NOAEL, proximity to the LOAEL region is not known, and the use of the NOAEL to derive an MRL would yield a value that is in the range of the selenium RDA (approximately 0.8 $\mu\text{g/kg/day}$) (NAS 2000) and below the chronic oral MRL derived below.

- An MRL of 0.005 mg/kg/day (5 $\mu\text{g/kg/day}$) has been derived for chronic oral exposure (>365 days) to selenium.

This MRL is based upon a study by Yang and Zhou (1994), who examined of a group of five individuals who were recovering from selenosis, and who were drawn from a larger population from an area of China where selenosis occurred (Yang et al. 1989a, 1989b). The study collected data on selenium levels in the diet, blood, nails, hair, urine, and milk of residents at three sites with low, medium, and high selenium, and compared the incidence of clinical symptoms of selenosis (morphological changes in fingernails)

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with dietary intake of selenium and selenium levels in blood. The average adult body weight was 55 kg (Yang et al., 1989b). It was found that selenium levels in blood corresponded to the dietary intake of selenium, and that symptoms of selenosis occurred at or above a selenium intake level of 910 µg/day (0.016 mg/kg/day) (Yang et al. 1989a). In 1992, Yang and Zhou (1994) reexamined five individuals from the high selenium site who had been suffering from symptoms of selenosis (loss of fingernails and hair), but were recovering (nails were regrowing). Since their earlier report, the living conditions of the population had improved; they had been cautioned against consuming high selenium foods, and part of their diet from locally produced corn had been replaced with rice or cereals. Yang and Zhou (1994) found that the concentration of selenium in the blood of these individuals had fallen from 1,346 µg/L (measured in 1986) to 968 µg/L (measured in 1992). Using a regression equation derived from the data in an earlier report (Yang et al. 1989b), it was calculated that the dietary intake of selenium associated with selenosis in these individuals was 1,270 µg/day, while an intake of 819 µg Se/day (was associated with recovery (Yang and Zhou 1994).

The chronic oral MRL is based on a NOAEL of 819 µg/day (0.015 mg/kg/day) for disappearance of symptoms of selenosis in recovering individuals (Yang and Zhou 1994) and uses an uncertainty factor of 3 for human variability. An uncertainty factor of 3 was considered appropriate because the individuals in this study were sensitive individuals drawn from a larger population and because of supporting studies, as discussed in Appendix A. The NOAEL used to derive the MRL is consistent with NOAELs observed for other human populations (Longnecker et al. 1991). The MRL is about 2.5–5 times higher than normal selenium intake levels of 71–152 µg/day (approximately 0.001–0.002 mg/kg/day) (DHHS 2002; FDA 1982a; Levander 1987; Pennington et al. 1989; Schrauzer and White 1978; Schubert et al. 1987; Welsh et al. 1981), and approximately 6 times greater than the RDA for selenium of 55 µg/day (~0.0008 mg/kg/day) (NAS 2000). The MRL does not represent a threshold for toxicity, but a daily intake that ATSDR considers to be safe for all populations. The exact point above the MRL at which effects might occur in sensitive individuals is uncertain.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of selenium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Selenium is a naturally occurring element that is widely distributed in rocks and soils. Although selenium has been reported at hazardous waste sites where it can occur in many forms, analysis of specific forms present at these sites has not been performed, and it is unclear how much selenium is present in some of the sites. Selenium has multiple oxidation states (valence states) including -2, 0, +4, and +6. The type of selenium found is a result of its oxidation state, which may vary according to ambient conditions, such as pH and microbial activity.

Elemental selenium (selenium[0]) is rarely found naturally, but it is stable in soils. Selenates (selenium[+6]) and selenites (selenium[+4]) are water soluble and can be found in water. Sodium selenate is among the most mobile forms of selenium because of its high solubility and inability to adsorb to soil particles. More insoluble forms, such as elemental selenium, are less mobile; therefore, there is less risk for exposure. Because of greater bioavailability, water-soluble selenium compounds are probably more toxic than elemental selenium by any route. Selenium is found in nature complexed with multiple compounds, and although various forms are discussed in the profile, many others exist. Some plants, such as alfalfa, yeasts, white grain, and cruciferous species (e.g., mustard, cabbage, broccoli, and cauliflower), are efficient accumulators of selenium. Plants can contain organic selenium primarily in the form of the amino acids, selenomethionine and selenocysteine, along with the dimethyl selenides. Elemental selenium can be oxidized to form selenium dioxide. While the products of oxidation might be expected at the soil surface, elemental selenium would be the expected predominant form in soils or sediments where anaerobic conditions exist. Selenium sulfides, used in some anti-dandruff shampoos, are not very water soluble and, therefore, like elemental selenium, are relatively immobile in the environment.

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Much of the selenium released to the environment comes from the burning of coal and other fossil fuels, and from other industrial processes such as the production of rubber. For more information on the physical and chemical properties of selenium, see Chapter 4. For more information on the potential for human exposure, see Chapter 6.

In humans and animals, selenium is an essential nutrient that plays a role in protecting tissues from oxidative damage as a component of glutathione peroxidase. It is also found in the deiodinases, including type I and II iodothyronine 5'-deiodinase, which convert thyroxine to triiodothyronine and in thioredoxin reductase, which catalyses the NADPH-dependent reduction of the redox protein thioredoxin. The biologically active form of selenium in these enzymes is the modified amino acid, selenocysteine. Humans and animals can be exposed to increased amounts of selenium through the use of dietary supplements containing selenium. The nutritional role of selenium is further discussed in Section 3.4. Although selenium is an essential nutrient, exposure to high levels via inhalation or ingestion may cause adverse health effects. The mechanism by which selenium exerts toxic effects is unknown, but existing theories are discussed in Section 3.5. Most of the studies available on health effects involve exposure to selenite, selenate, and a form found in foods (selenomethionine).

Several factors should be considered when evaluating the toxicity of selenium compounds. The purity and grade of the particular test substance used in the testing are important factors. For example, in studies of selenium sulfide compounds, the amounts of mono- and disulfides are often not specified by the study authors. The solubility and the particle size of selenium compounds can also influence their toxicity.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in Tables 3-1, 3-2, and 3-3 and illustrated in Figures 3-1, 3-2, and 3-3. The points in the figures showing no-observed-adverse-effect

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levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. The oral doses presented in these tables and figures, as well as those included in the text of this chapter, are expressed on a per kg of body weight basis. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables (Tables 3-1, 3-2, and 3-3) and figures (Figures 3-1, 3-2, and 3-3) may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for selenium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, chronic bronchitis, or multiple chemical exposure. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Table 3-1 and Figure 3-1 describe the health effects observed in experimental animals that inhaled elemental selenium dust or hydrogen selenide. Studies of other forms of selenium are not presented in the LSE tables and figures (Table 3-1 and Figure 3-1) because either the reporting of the studies was incomplete or no studies on other forms were located. All doses are expressed in terms of total selenium.

3.2.1.1 Death

No studies were located regarding death in humans after inhalation of elemental selenium or selenium compounds.

In animals, the acute lethality of hydrogen selenide and elemental selenium dust when inhaled has been investigated. In guinea pigs exposed to hydrogen selenide for 2, 4, or 8 hours, 5/16 died within 10 days of exposure at 12 mg selenium/m³, 3/16 died at 6 mg selenium/m³, and 8/16 died at 6 mg selenium/m³, respectively (Dudley and Miller 1941).

No deaths were observed among rabbits or guinea pigs exposed to elemental selenium dust at levels of 31 mg selenium/m³ for 4 hours every other day for 8 exposure days (Hall et al. 1951). Higher levels were not tested.

Table 3-1 Levels of Significant Exposure to Selenium - Inhalation

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
ACUTE EXPOSURE							
Death							
1	Gn Pig (NS)	4 hr				6 (3/16 died)	Dudley and Miller 1941 hydrogen selenide
2	Gn Pig (NS)	8 hr				1 (8/16 died)	Dudley and Miller 1941 hydrogen selenide
3	Gn Pig (NS)	2 hr				12 (8/16 died)	Dudley and Miller 1941 hydrogen selenide
Systemic							
4	Rat (NS)	8 hr	Resp			33 F (pulmonary hemorrhage, pneumonitis)	Hall et al. 1951 elemental
			Hepatic		33 F (congestion; mild central atrophy)		
			Renal	33 F			
			Endocr	33 F			
			Bd Wt	33 F			
5	Gn Pig (NS)	4 hr	Resp			8 (pneumonitis)	Dudley and Miller 1941 hydrogen selenide
			Cardio	8			
			Hepatic		8 (fatty metamorphosis, increased liver weight)		
			Renal	8			
			Endocr	8			

Table 3-1 Levels of Significant Exposure to Selenium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
6	Gn Pig (NS)	8 d 4hr/2d	Resp		33 M (mild congestion; mild to moderate interstitial pneumonitis; slight emphysema)		Hall et al. 1951 elemental
			Cardio	33 M			
			Hepatic		33 M (congestion; central atrophy; fatty metamorphosis)		
			Renal	33 M			
			Bd Wt	33 M			
7	Rabbit (NS)	8 d 4hr/2d	Resp		33 F (congestion, mild pneumonitis)		Hall et al. 1951 elemental
			Cardio	33 F			
			Hepatic	33 F			
			Renal	33 F			
			Bd Wt	33 F			
8	Immuno/ Lymphoret Rat (NS)	8 hr		33			Hall et al. 1951 elemental

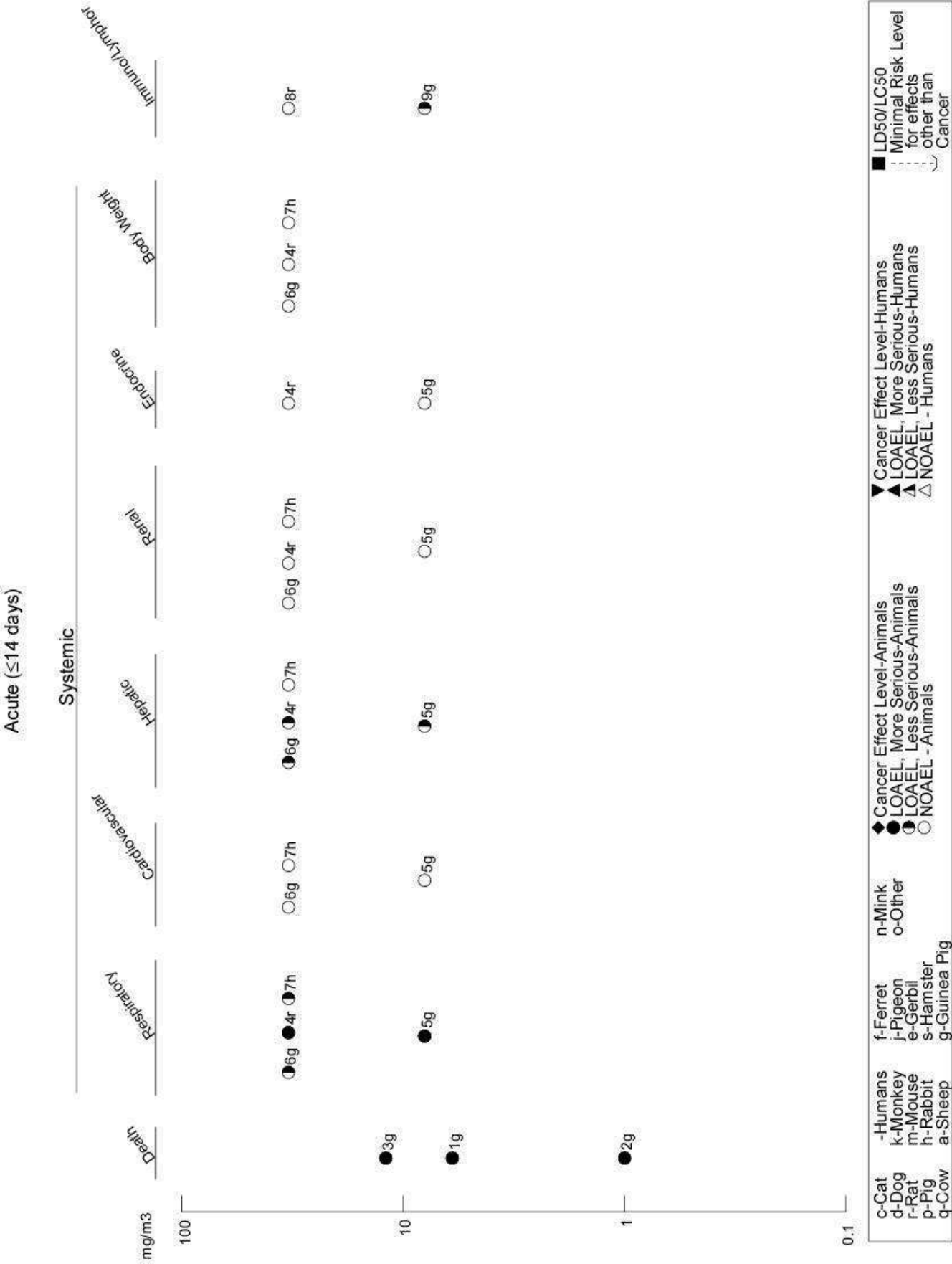
Table 3-1 Levels of Significant Exposure to Selenium - Inhalation (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)	
9	Gn Pig (NS)	4 hr			8 (splenic hyperplasia)		Dudley and Miller 1941 hydrogen selenide

a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); (F) = feed; Endocr = endocrine; F = female; gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory

Figure 3-1. Levels of Significant Exposure to Selenium - Inhalation



All LOAEL values from each reliable study for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The selenium compounds that are most likely to be encountered in air in occupational settings are dusts of elemental selenium, hydrogen selenide, and selenium dioxide. Other volatile selenium compounds (e.g., dimethyl selenide, dimethyl diselenide) might be encountered in some naturally occurring situations. Because selenium is converted from one form to another, as in plant biosynthesis of selenoamino acids, it is not clear which specific forms may be encountered at hazardous waste sites. If a hazardous waste site specifically contains deposits of compounds of selenium, those compounds could be released off-site in dust or air. Toxicity data for exposures via inhalation are available for elemental selenium, selenium dioxide, selenium oxychloride, hydrogen selenide, and dimethyl selenide. Because there are few studies of inhalation of selenium of any single form, all available studies of inhalation exposures to selenium compounds will be included in this discussion.

In studies of human occupational exposures, it appears that the respiratory tract is the primary site of injury after inhalation of selenium dust or selenium compounds, but gastrointestinal (possibly due to swallowed selenium) and cardiovascular effects, as well as irritation of the skin and eyes, also occur. Little of the available information for humans, however, relates health effects exclusively to measured concentrations of the selenium dust or compounds because of the possibility of concurrent exposures to multiple substances in the workplace. In animals, the respiratory tract is also the primary site of injury following inhalation exposure to selenium dust and hydrogen selenide. Hematological and hepatic effects have also been noted in animals. Inhalation data from laboratory animal studies are available only for acute exposures.

No information was located regarding hematological, musculoskeletal, dermal, or ocular effects in humans or laboratory animals after inhalation exposure to selenium or selenium compounds. The systemic effects that have been observed after inhalation exposure are discussed below. The highest NOAEL values and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

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Respiratory Effects. In humans, the respiratory system is the primary site of injury after inhalation of elemental selenium or selenium compounds. The largest number of reported human exposures occurred in occupational settings, especially in industries that extract, mine, treat, or process selenium-bearing minerals and in industries that use selenium or selenium compounds in manufacturing. The reports of occupational exposure do not link observed symptoms to specific air concentrations of elemental selenium or selenium compounds. Several reports, however, have noted common effects associated with inhalation exposure in occupational settings.

Selenium dioxide is formed when selenium is heated in air. Direct exposure to selenium dioxide is, therefore, primarily an occupational hazard and not likely to be a risk at hazardous waste sites. Selenium dioxide forms selenious acid on contact with water, including perspiration, and can cause severe irritation. Acute inhalation of large quantities of selenium dioxide powder can produce pulmonary edema as a result of the local irritant effect on alveoli (Glover 1970). Bronchial spasms, symptoms of asphyxiation, and persistent bronchitis have been noted in workers briefly exposed to high concentrations of selenium dioxide (Wilson 1962). Kinnigkeit (1962) reported that selenium dioxide concentrations of 0.007–0.05 mg selenium/m³ in a selenium rectifier plant produced slight tracheobronchitis in 9 of 62 exposed workers.

Hydrogen selenide, a highly poisonous selenium compound, is a gas at room temperature, with a density much higher than air. Selenium oxychloride, also highly toxic, is more irritating and corrosive to the human respiratory tract than are other forms of selenium because the compound hydrolyzes to hydrogen chloride (HCl), which can then form hydrochloric acid in humid air and in the respiratory tract (Dudley 1938). Hydrogen selenide and selenium oxychloride are occupational exposure hazards that are not expected to be much of a concern at hazardous waste sites.

Acute inhalation exposure to elemental selenium dust, possibly including some selenium dioxide, in occupational settings has been shown to irritate mucous membranes in the nose and throat and produce coughing, nosebleed, loss of olfaction, and in heavily exposed workers, dyspnea, bronchial spasms, bronchitis, and chemical pneumonia (Clinton 1947; Hamilton 1949). Chronic exposure of 40 workers at a copper refinery produced increased nose irritation and sputum (Holness et al. 1989). The exact concentration of selenium was not given, but the concentration was reported to exceed 0.2 mg selenium/m³. Confounding variables in this study include concurrent exposure to several other metals including copper, nickel, silver, lead, arsenic, and tellurium.

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In experimental animals, the respiratory tract is the primary site of injury following acute inhalation exposure to elemental selenium and selenium compounds. Rats exposed to selenium fumes (selenium concentration and particle size were not reported) for 2–16 minutes experienced moderate to severe respiratory effects, including hemorrhage and edema of the lungs (Hall et al. 1951). Rats exposed to selenium dust (average particle diameter, 1.2 μm) at levels of 33 mg selenium/ m^3 for 8 hours experienced severe respiratory effects, including hemorrhage and edema of the lungs, and several animals died (Hall et al. 1951). Histopathological examinations of surviving animals revealed chronic interstitial pneumonitis. Acute exposure of rabbits and guinea pigs to selenium dust (average particle diameter, 1.2 μm) at a concentration of 33 mg selenium/ m^3 resulted in mild interstitial pneumonitis or congestion, and slight emphysema in both species (Hall et al. 1951). Other histological findings included vascular lymphocytic infiltration and intra-alveolar foci of large macrophages.

Acute inhalation exposure of guinea pigs to 8 mg selenium/ m^3 as hydrogen selenide for 4 hours produced diffuse bronchopneumonia and pneumonitis (Dudley and Miller 1941). The investigators do not indicate if any of these guinea pigs died as a result of the exposure. Histologic examination of animals that died following exposure to higher concentrations revealed thickening of the alveolar walls and congestion of alveolar capillaries (Dudley and Miller 1937). In contrast, 1-hour exposure of rats to 25,958 mg selenium/ m^3 as dimethyl selenide produced only minor effects (increased weight of lung and liver) 1 day postexposure. These changes disappeared by 7 days postexposure (Al-Bayati et al. 1992). Enzymatic methylation of selenium compounds is the primary route of detoxification and may explain the low toxicity of dimethyl selenide (Al-Bayati et al. 1992). Although this form of selenium is environmentally relevant since it is formed in soil, plants, and microorganisms, dimethyl selenide appears to be relatively nontoxic in comparison to occupational exposure to hydrogen selenide.

The effects of intratracheal instillation of selenium on pulmonary function may be dependent on the form in which it is supplied (Nonavinakere et al. 1999). Instillation of 0.06 mg selenium/100 g body weight as selenium dioxide produced a significant decrease in respiratory rate and a significant increase in lung resistance compared with controls. Instillation with 0.06 mg selenium/110 g body weight as seleno-L-methionine also produced a decrease in respiratory rate and an increase in lung resistance, but the values were not significantly different from controls.

Intratracheal instillation of 0.3 mg selenium as sodium selenite in male Hartley-guinea pigs decreased dynamic-lung-compliance and increased pulmonary resistance compared with control animals instilled with saline (Bell et al. 1997). Analysis of bronchoalveolar-lavage fluid showed increased activities of

3. HEALTH EFFECTS

lactate dehydrogenase, β -glucuronidase, alkaline phosphatase, and protein, suggesting damage to lung tissue.

Histological analysis of guinea pigs that received single intratracheal instillations of 0.3 mg selenium as sodium selenite found mild acute inflammation in approximately one-third of the lung tissue and a noticeable amount of sloughed epithelium and mucus within the bronchi (Bell et al. 2000). Lungs of animals treated with 0.06 mg selenium showed neutrophils aggregated in the alveoli and some dilation of the alveoli suggestive of emphysema. Relative lung weights and the ratio of wet/dry lung weight were increased in the selenium-treated animals compared with controls; the increase was only significant for those receiving the higher dose of selenium. Leukocyte counts in bronchoalveolar-lavage fluid were decreased for selenium-treated animals compared with controls, and the difference was significant for the animals receiving 0.3 mg selenium, but not the 0.06 mg dosage.

No studies were located regarding respiratory effects in animals after intermediate or chronic inhalation of selenium or selenium compounds.

Cardiovascular Effects. Several workers experienced symptoms of shock, including lower blood pressure and elevated pulse rates, following an acute exposure (at most 20 minutes) to selenium dioxide fumes resulting from a fire (Wilson 1962). The subjects were treated with oxygen and inhalation of ammonia vapor, and pulse rates were normalized within 3 hours.

Cardiovascular effects were not observed in guinea pigs exposed to hydrogen selenide at 8 mg selenium/m³ for 4 hours (Dudley and Miller 1941), or in guinea pigs and rabbits exposed to elemental selenium dust (average particle diameter, 1.2 μ m) every other day at 33 mg selenium/m³ for eight 4-hour exposure periods (Hall et al. 1951).

Gastrointestinal Effects. Vomiting and nausea were reported in workers exposed to high concentrations of selenium dioxide for a maximum of 20 minutes during a fire (Wilson 1962). Stomach pain was frequently reported by workers exposed to elemental selenium and selenium dioxide at a selenium rectifier plant (Glover 1967), and by copper refinery workers exposed to an unspecified form of selenium (Holness et al. 1989). Exposure concentrations were not reported for the rectifier plant, but were >0.2 mg selenium/m³ at the copper refinery.

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No studies were located regarding gastrointestinal effects in animals after inhalation of selenium or selenium compounds.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation of selenium or selenium compounds.

Hepatotoxicity has been observed in experimental animals following inhalation exposure to elemental selenium dust and to hydrogen selenide. One month after an 8-hour exposure to elemental selenium dust at a level of 33 mg selenium/m³, most rats exhibited slight liver congestion and a few exhibited mild centrilobular atrophy (Hall et al. 1951). In contrast, 1 week after exposure to 25,958 mg selenium/m³ as dimethyl selenide for 1 hour, rats showed no observable changes in the liver (Al-Bayati et al. 1992). Three weeks following acute exposure to elemental selenium dust at a level of 33 mg selenium/m³ for 4 hours every other day for 8 days, 4/10 guinea pigs exhibited slight hepatic congestion with mild central atrophy and 2/10 showed some fatty hepatocellular degeneration (Dudley and Miller 1941). In contrast, exposure of guinea pigs to lower concentrations of selenium (8 mg/m³), as hydrogen selenide, for a single 4-hour period produced mild fatty hepatocellular metamorphosis (Dudley and Miller 1941).

Renal Effects. No studies were located regarding renal effects in humans after inhalation of selenium or selenium compounds.

The kidneys do not appear to be affected in guinea pigs (Dudley and Miller 1941; Hall et al. 1951) after acute inhalation exposure to 33 mg selenium/m³ as hydrogen selenide for 8 hours or to 8 mg selenium/m³ as elemental selenium dust for 4 hours. Likewise, the kidneys were not affected in rabbits following acute inhalation exposure to 33 mg selenium/m³ as hydrogen selenide for 8 hours (Hall et al. 1951) or in rats following acute inhalation exposure to 25,958 mg selenium/m³ as dimethyl selenide for 1 hour or to 33 mg selenium/m³ as hydrogen selenide for 8 hours (Al-Bayati et al. 1992; Hall et al. 1951).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation of selenium or selenium compounds.

No histopathological changes in the adrenal gland were observed in guinea pigs exposed to hydrogen selenide at 8 mg selenium/m³ for 4 hours (Dudley and Miller 1941) or in rats exposed to elemental selenium at 33 mg selenium/m³ for 8 hours (Hall et al. 1951).

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Body Weight Effects. No studies were located regarding effects on body weight in humans following inhalation of selenium or selenium compounds.

No effects on body weight were observed in guinea pigs following a single 8-hour exposure to elemental selenium at 33 mg selenium/m³ or in guinea pigs and rabbits exposed to elemental selenium dust at 33 mg selenium/m³ every other day for 4 hours for a total of eight exposures (Hall et al. 1951).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after inhalation exposure to selenium or selenium compounds.

Lymphoid hyperplasia was noted in the spleen of guinea pigs following a single 4-hour exposure at 8 mg selenium/m³ as hydrogen selenide (Dudley and Miller 1941). Histopathological changes in the spleen were not observed in guinea pigs exposed to elemental selenium dust (average particle diameter, 1.2 µm) at 33 mg selenium/m³ for 8 hours (Hall et al. 1951). Injury to the spleen was observed in guinea pigs following exposure for 4 hours, every other day, for 8 days to elemental selenium dust at a level of 33 mg selenium/m³ (Hall et al. 1951). Specific effects included congestion of the spleen, fissuring red pulp, and increased polymorphonuclear leukocytes (Hall et al. 1951).

3.2.1.4 Neurological Effects

Information concerning possible neurological effects caused by inhalation of selenium or selenium compounds is limited. Severe frontal headaches were reported by workers exposed during an accident to high concentrations of selenium fumes (compound not stated) for approximately 2 minutes (Clinton 1947). Workers at a selenium rectifier plant reported symptoms of malaise and irritability when working with selenium (exposure was probably to selenium dioxide and elemental selenium, but the form was not stated) (Glover 1967). The symptoms resolved whenever the workers were moved to other work. Urinary concentrations of selenium were about 0.08 mg/L, compared to 0.024–0.034 mg/L in unexposed workers.

No studies were located regarding neurological effects in animals after inhalation of selenium or selenium compounds.

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No studies were located regarding the following health effects in humans or animals after inhalation exposure to selenium or selenium compounds:

3.2.1.5 Reproductive Effects**3.2.1.6 Developmental Effects****3.2.1.7 Cancer**

There are no epidemiologic data that support a causal association between the inhalation of elemental selenium dusts or selenium compounds and the induction of cancer in humans (Gerhardsson et al. 1986; Wester et al. 1981). In one study, postmortem samples were collected from copper smelter workers who were exposed to several different airborne compounds, including selenium compounds. Samples from lung cancer cases had lower concentrations of selenium in lung tissue than samples from controls or from workers who had died from other causes (Gerhardsson et al. 1986). In another autopsy study of smelter workers, Wester et al. (1981) found that the selenium concentrations in kidney tissues from workers who had died of malignancies were lower than the selenium concentrations in kidney tissues from workers who died of other causes. Further discussions regarding the cancer protective effects of selenium can be found in Section 3.2.2.7.

No studies were located regarding carcinogenic effects in laboratory animals after inhalation exposure to selenium or selenium compounds.

3.2.2 Oral Exposure

Table 3-2 and Figure 3-2 describe the health effects observed in humans and experimental animals associated with dose and duration of oral exposure to selenium and selenium compounds (i.e., elemental selenium dust, selenium dioxide dissolved in water [selenious acid], sodium selenate, sodium selenite, potassium selenate, and dietary selenium compounds, which include selenoamino acids). All doses for these compounds are expressed in terms of total selenium. Table 3-3 and Figure 3-3 describe health effects observed in laboratory animals following oral exposure to selenium sulfides (SeS_2 and SeS) at varying doses and exposure durations. All doses for selenium sulfide compounds are expressed in terms

Table 3-2 Levels of Significant Exposure to Selenium - Oral

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	once (G)				6700 M (LD50)	Cummins and Kimura 1971 elemental
2	Rat (Sprague-Dawley)	once (GW)				7 M (LD50)	Cummins and Kimura 1971 selenite
3	Rat (Sprague-Dawley)	14 d ad lib (W)				0.418 F (7/12 died)	NTP 1996 sodium selenate
4	Rat (NS)	once (G)				4.8 F (LD50)	Pletnikova 1970 selenite
5	Rat (Wistar)	once (GW)				48 (LD50)	Singh and Junnarkar 1991 selenium dioxide
6	Mouse (NS)	once (G)				3.2 M (LD50)	Pletnikova 1970 selenite
7	Mouse (ICR)	once (G)				35.9 M (LD50)	Sayato et al. 1993 D,L-selenocystine
8	Mouse (Swiss)	once (GW)				16 M (LD50)	Singh and Junnarkar 1991 selenium dioxide
9	Gn Pig (NS)	once (G)				2.3 F (LD50)	Pletnikova 1970 selenite

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
10	Rabbit (NS)	once (G)				1 F (LD50)	Pletnikova 1970 selenite
Systemic							
11	Rat (Sprague-Dawley)	14 d ad lib (W)	Bd Wt	0.251 F		0.418 F (significant (36%) reduction in body weight)	NTP 1996 sodium selenate
12	Mouse (BALB/c)	14 d ad lib (W)	Hemato	0.38 M	0.82 M (significant increase in red blood cell count)		Johnson et al. 2000 Selenite
			Hepatic	0.38 M	0.82 M (significant decrease in relative liver weight)		
			Renal	0.17 M	0.38 M (significant increase in relative kidney weight)		
			Bd Wt	0.38 M	0.82 (significant decrease in body weight gain)		
13	Mouse (BALB/c)	14 d ad lib (W)	Hemato	1.36 M			Johnson et al. 2000 selenomethionine
			Hepatic	1.36 M			
			Renal	1.36 M			
			Bd Wt	1.36 M			

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
14	Pig (NS)	5 d	Resp	1.25			Panter et al. 1996 organic
			Cardio	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Dermal	1.25			
			Bd Wt			1.25 (5% loss of body weight)	
15	Mouse (BALB/c)	14 d ad lib (W)		0.38 M	0.82 M (increased proliferation of splenic lymphocytes and LPS-induced production of TNF alpha and IL-1beta)		Johnson et al. 2000 Selenite
16	Mouse (BALB/c)	14 d ad lib (W)		1.36 M			Johnson et al. 2000 selenomethionine
17	Mouse (Swiss)	once (GW)			1.6 (decreased activity, muscle tone, touch response, respiration; hypothermia)		Singh and Junnarkar 1991 selenium dioxide
18	Mouse (BALB/c)	14 d ad lib (W)		0.24 M	0.58 M (significant increase in the levels of striatal dihydroxyphenylacetic acid and homovanillic acid)		Tsunoda et al. 2000 Selenite

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/Duration/ Frequency (Specific Route)	LOAEL				Reference Chemical Form
			System	NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
19	Mouse (BALB/c)	14 d ad lib (W)		1.96 M			Tsunoda et al. 2000 Organic selenium
20	Pig (NS)	10 d 1x/d (C)				1.3	Wilson et al. 1989 (hypoactivity, focal symmetrical poliomalacia, histopathological lesions in brain and spinal cord)
Developmental							
21	Hamster (Syrian LKV)	once Gd 8 (GW)		7.1		7.9	Ferm et al. 1990 (encephalocele; decreased crown-rump length)
22	Hamster (Syrian LKV)	once Gd 8 (GW)				7.1	Ferm et al. 1990 selenate
23	Hamster (Syrian LKV)	once Gd 8 (GW)			5.9 (decreased fetal crown-rump length)		Ferm et al. 1990 selenomethionine
INTERMEDIATE EXPOSURE							
Death							
24	Rat (Sprague- Dawley)	6 wk ad lib (F)				0.48 M (1/8 died)	Halverson et al. 1966 selenite
25	Rat (Sprague- Dawley)	6 wk ad lib (F)				0.4 M (1/8 died)	Halverson et al. 1966 organic
26	Rat (Fischer- 344)	13 wk (W)				2.54 (20/20 died)	NTP 1994 selenate

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
27	Rat (Fischer- 344) (W)	13 wk				NTP 1994 selenite
28	Rat (Sprague- Dawley)	4-6 wk ad lib (W)				Palmer and Olson 1974 selenite
29	Rat (Sprague- Dawley)	4-6 wk ad lib (W)				Palmer and Olson 1974 selenate
30	Rat (Wistar)	1 yr daily ad lib (W)				Rosenfeld and Beath 1954 selenate
31	Rat (BLU:[LE])	365 d (W)				Schroeder and Mitchener 1971a selenite
32	Mouse (ICR)	30 d 6d/wk (G)				Sayato et al. 1993 D,L-selenocystine
33	Systemic Human	20 wk (IN)	Endocr	0.001		Duffield et al. 1999
34	Human	102d (F)	Endocr	0.0039 M		Hawkes and Turek 2001 dietary

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
35	Human	120d (F)	Hemato	0.004 M			Hawkes et al. 2001 dietary
36	Monkey (Macaca fascicularis)	gd 20-50 1x/d (GW)	Gastro	0.025 F	0.15 F (vomiting)		Tarantal et al. 1991 selenomethionine
37	Rat (Wistar)	110 d ad lib (F)	Bd Wt	0.025 F	0.15 F (increased weight loss)		Behne et al. 1992 sodium selenite
38	Rat (Wistar)	110 d ad lib (F)	Endocr	0.105 M	0.105 M (significant reduction in type I deiodinase activity)		Behne et al. 1992 selenomethionine
39	Rat (Sprague-Dawley)	2 mo ad lib (F)	Bd Wt	0.105 M	0.118 M (significant reduction in type I deiodinase activity)	0.118 M (significant reduction in body weight (15%))	Behne et al. 1992 selenomethionine
			Hepatic	0.1 M	0.2 M (nodular regenerative hyperplasia, increased relative liver weight)		Bioulac-Sage et al. 1992 selenite
			Bd Wt	0.2 M			

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
40	Rat (Sprague-Dawley)	8 wk (F)	Resp	0.45 M			Chen et al. 1993 selenite
			Cardio	0.45 M			
			Gastro	0.45 M			
			Hepatic		0.45 M (diffuse panlobular vacuolar accumulation of glycogen and lipid)		
			Renal	0.45 M			
			Bd Wt		0.25 M (final body weights about 14% lower than controls)	0.35 M (final body weights about 29% lower than controls)	
41	Rat (Sprague-Dawley)	40 d ad lib (F)	Hemato	0.27 M			Eder et al. 1995 sodium selenite
			Endocr	0.026 M	0.055 M (significant reduction in serum tri-iodothyronine levels)		
			Bd Wt	0.27 M			
42	Rat (Sprague-Dawley)	6 wk ad lib (F)	Hemato	0.24 M	0.32 M (23% decrease in hemoglobin)	0.56 M (79% decrease in hemoglobin)	Halverson et al. 1966 organic
			Hepatic		0.4 M (6-fold increase in bilirubin)		
			Endocr	0.32 M	0.4 M (pancreas weight 1.4 times greater than diet restricted controls)		
			Bd Wt	0.32		0.4 M (body weight gain 36% lower than controls)	

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
43	Rat (Sprague-Dawley)	6 wk ad lib (F)	Endocr		0.09 M (significant increase in serum TSH (~30%))		Hotz et al. 1997 sodium selenate
			Bd Wt	0.09 M			
			Metab		0.09 M (significant increase in GSH-Px in kidney (~30%) and erythrocytes (~100%))		
44	Rat (Wistar)	3 mo 1x/d (F)	Hepatic		0.002 M (sporadic infiltrations of mononuclear cells in portal canals and weak activation of Kupffer cells)	0.005 M (distinct swelling of Kupffer cells in dilated sinusoidal vessels and necrotic areas comprising single groups of hepatocytes)	Kolodziejczyk et al. 2000

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
45	Rat (Fischer- 344) (W)	13 wk	Resp	1.57 M			NTP 1994 selenate
			Cardio	1.57 M			
			Gastro	1.57 M			
			Hemato	0.92 M	1.57 M (increased hematocrit and hemoglobin associated with decreased water intake)		
			Musc/skel	1.57 M			
			Hepatic	0.92 M	1.57 M (increased bile acids indicating cholestasis)		
			Renal	0.31 F	0.47 F (minimal papilla degeneration of the kidneys)		
			Endocr	1.57 M			
			Ocular	1.57 M			
			Bd Wt	0.47 F	0.88 F (body weights 10% less than controls)	1.35 F (body weights 29% less than controls, associated with decreased water intake)	

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
46	Rat (Fischer- 344) (W)	13 wk	Resp	1.67 F			NTP 1994 selenite
			Cardio	1.67 F			
			Gastro	1.67 F			
			Hemato	0.86 F	1.67 F (increased hematocrit associated with decreased water intake)		
			Musc/skel	1.67 F			
			Hepatic	1.67 F			
			Renal	0.28 F	0.5 F (mild papilla degeneration)		
			Endocr	1.67 F			
47	Rat (Sprague-Dawley)	23-29 d ad lib (W)	Ocular	1.67 F			NTP 1996 sodium selenate
			Bd Wt	0.98 M		1.59 M (body weights 34% less than controls; associated with decreased water intake)	
			Bd Wt	0.167 M ^b	0.293 M ^b (significant (11%) reduction in body weight)	0.418 ^b (significant (20% male, 39% female) reduction in body weight)	
				0.209 F	0.334 F		
48	Rat (Sprague-Dawley)	4-6 wk ad lib (W)	Hepatic			0.84 M (cirrhosis)	Palmer and Olson 1974 selenate
			Bd Wt		0.42 M (body weight gain 10% lower than controls)		

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
49	Rat (Sprague-Dawley)	6 wk ad lib (F)	Bd Wt	0.125 M			Salbe and Levander 1990a selenate
50	Rat (Sprague-Dawley)	6 wk ad lib (F)	Bd Wt	0.125 M			Salbe and Levander 1990a selenomethionine
51	Rat (Wistar)	3-6 wks ad lib (W)	Endocr		0.64 F (decreased somatomedin C)		Thorlacius-Ussing 1990 selenite
			Bd Wt			0.64 F (body weight gain 30% lower than controls)	
52	Rat (Wistar)	12-14 wk ad lib	Cardio			0.324 (degeneration of heart tissue with disruption of myofibrils and sodium sarcomeres)	Turan et al. 1999a
			Hepatic			0.324 (degeneration of liver tissue with dilation of sinusoidal capillaries)	
			Bd Wt		0.324 (significant decrease in body weight (17%))		
53	Mouse (ICR)	90 d (G)	Hepatic	2.4 M	4.7 M (increased serum aspartate aminotransferase and alanine aminotransferase)		Hasegawa et al. 1994 D,L-selenocystine
			Bd Wt	2.4 M	4.7 M (body weights 16% lower than controls)	7.1 M (body weights 22% lower than controls)	

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
54	Mouse (B6C3F1)	13 wk (W)	Resp	3.83 F			NTP 1994 selenite
			Cardio	3.83 F			
			Gastro	3.83 F			
			Hemato	3.83 F			
			Musc/skel	3.83 F			
			Hepatic	3.83 F			
			Renal	0.91 M	1.61 M (increased relative kidney weight; decreased water intake)		
			Endocr	3.83 F			
			Ocular	3.83 F			
			Bd Wt	1.61 M			
						3.31 M (body weights 20% lower than controls; decreased water intake)	

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
55	Mouse (B6C3F1)	13 wk (W)	Resp	7.17 F			NTP 1994 selenate
			Cardio	7.17 F			
			Gastro	7.17 F			
			Hemato	7.17 F			
			Musc/skel	7.17 F			
			Hepatic	7.17 F			
			Renal	1.07 M	1.87 M (increased kidney weight associated with decreased water intake)		
			Endocr	7.17 F			
56	Mouse (ICR)	30 d 6d/wk (G)	Ocular	7.17 F			Sayato et al. 1993 D,L-selenocystine
			Bd Wt	1.87	2.95 M (body weights 13% lower than controls; decreased water intake)	5.45 M (body weights 24% lower than controls; decreased water intake)	
			Hepatic	4.7 M	9.4 M (significant 2-3-fold increases in aspartate aminotransferase and alanine aminotransferase)		
			Renal	9.4 M			
			Bd Wt		9.4 M (final body weight about 13% lower than controls)	18.9 M (final body weight about 29% lower than controls)	

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
57	Mouse Balby	12 wk ad lib (F)	Hepatic		0.2 M (vacuolization of hepatocytes)		Skowerski et al. 1997a sodium selenite
58	Mouse Balby	12 wk ad lib (F)	Cardio		0.2 M (cardiocytes have numerous damaged mitochondria, large number of lipid droplets and numerous lysosomes)		Skowerski et al. 1997b sodium selenite
59	Rabbit (New Zealand)	3 mo ad lib (F)	Bd Wt	0.2 M			
			Cardio			0.137 (disruption of myofibrils, irregular sarcomeres, and disorganization of bands in sarcomeres)	Turan et al. 1999b sodium selenite
			Hemato	0.137			
			Bd Wt	0.137			
60	Pig (mixed breed)	8 wk ad lib (F)	Hepatic		1.1 (vacuolar degeneration, portal fibrosis)		Baker et al. 1989 selenate
			Dermal		1.1 (cracked hoof walls)		
			Bd Wt			1.1 (body weight gain 83% lower than controls, accompanied by decreased food intake)	

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
61	Pig (NS)	35 d ad lib (F)	Dermal	0.014	0.25 (hoof cracking)		Mahan and Magee 1991 selenite
			Bd Wt	0.25		0.47 (body weight gain 78% lower than controls, accompanied by decreased food intake)	
62	Pig (crossbred L x Y)	8 wk ad lib (F)	Hepatic	0.33			Mihailovic et al. 1992 selenite
			Dermal	0.33	0.59 (hoof cracking, alopecia, redness of skin, petechiae)	0.59 (atrophic cirrhosis)	
63	Pig (NS)	31 +/- 14 d	Cardio	1.25			Panter et al. 1996 D,L-selenomethionine
			Hepatic	1.25			
			Renal	1.25			
			Dermal		1.25 (symmetrical hair loss, dry scaling skin, cracked overgrown hooves 3/5 pigs)		
			Bd Wt		1.25 (body weight gain 15% less than controls)		

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
64	Pig (NS)	16 +/- 16 d	Resp	1.25			Panter et al. 1996 selenate
			Cardio	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Dermal		1.25 (symmetrical hair loss, dry scaling skin, cracked overgrown hooves 1/5 pigs)		
			Bd Wt			1.25 (body weight gain 22% less than controls)	
65	Pig (NS)	34 d ad lib (F)	Cardio			0.46 (vacuolation, pyknosis of nuclei)	Stowe et al. 1992 NS
			Musc/skel			0.46 (hyperplasia of sarcolemma nuclei; disintegration of myofibrils)	
66	Pig (Duroc)	NS ad lib (F)	Dermal		0.4 F (2/10 alopecia; 1/10 hoof separation)		Wahlstrom and Olson 1959b selenite
			Bd Wt	0.4 F			

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
67	Cattle Hereford	120 d 1x/d (F)	Resp	0.808 M			O'Toole and Raisbeck 1995 selenomethionine
			Cardio	0.808 M			
			Gastro	0.808 M			
			Musc/skel	0.808 M			
			Hepatic	0.808 M			
			Renal	0.808 M			
			Endocr	0.808 M			
			Dermal	0.158 M	0.288 M (mild parakeratosis of hoof)	0.808 M (severe parakeratosis and epithelial hyperplasia of hoof)	
			Ocular	0.808 M			

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
68	Cattle Hereford	120 d 1x/d (F)	Resp	0.808 M			O'Toole and Raisbeck 1995 sodium selenite
			Cardio	0.808 M			
			Gastro	0.808 M			
			Musc/skel	0.808 M			
			Hepatic	0.808 M			
			Renal	0.808 M			
			Endocr	0.808 M			
			Dermal	0.288 M		0.808 M (mild parakeratosis of hoof)	
69	Human	120d (F)	Ocular	0.808 M			Hawkes et al. 2001 dietary
				0.004 M			
70	Rat (Sprague- Dawley)	10 wk ad lib (W)					Koller et al. 1986 selenite
					0.7 F (decreased delayed-type hypersensitivity; increased thymus weight)		
71	Mouse (BALB/c)	47 d ad lib (W)					Raisbeck et al. 1998 selenocystine
					0.173 (reduced B-cell function and OVA-specific antibody concentration)		

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
72	Mouse (BALB/c)	47 d ad lib (W)			0.173	(reduced B-cell function and OVA-specific antibody concentration)	Raisbeck et al. 1998 selenomethionine
73	Mouse (BALB/c)	47 d ad lib (W)			0.173	(reduced OVA-specific antibody concentration)	Raisbeck et al. 1998 sodium selenite
74	Cattle Hereford	120 d 1x/d (F)		0.808 M			O'Toole and Raisbeck 1995 selenomethionine
75	Cattle Hereford	120 d 1x/d (F)		0.808 M			O'Toole and Raisbeck 1995 sodium selenite
Neurological							
76	Human	120 d (F)		0.0048 M			Hawkes and Hornbostel 1996 selenomethionine
77	Monkey (Macaca fascicularis)	30 d 1x/d (GW)		0.08	0.12 F (hypothermia)		Cukierski et al. 1989 selenomethionine
78	Pig (mixed breed)	7 wk ad lib (F)				1.3	Baker et al. 1989 (tetraplegia, poliomyelomalacia) organic
79	Pig (crossbred L x Y)	8 wk ad lib (F)		0.33		0.59	Mihalovic et al. 1992 (hind limb paresis, hind limb ataxia, symmetric poliomyelomalacia of the ventral horn of the spinal cord) selenite

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	LOAEL				Reference Chemical Form
			System	NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
80	Pig (NS)	20-42d ad lib (F)		1		2.1	Wilson et al. 1983 (poliomyelomalacia, paralysis, diffuse gliosis of the spinal cord) selenite
81	Cattle Hereford	120 d 1x/d (F)		0.808 M			O'Toole and Raisbeck 1989 selenomethionine
82	Cattle Hereford	120 d 1x/d (F)		0.808 M			O'Toole and Raisbeck 1989 sodium selenite
83	Human	Reproductive 102d (F)		0.0039 M			Hawkes and Turek 2001 dietary
84	Monkey (Macaca fascicularis)	30 d 1x/d (GW)		0.06 F	0.08 F (altered menstrual cycle)		Cukierski et al. 1989 selenomethionine
85	Rat (Wild)	5 wk (F)			0.1 M (3.9% abnormal sperm; decrease in live sperm)	0.2 M (24.6% abnormal sperm; decreased live sperm, and sperm motility; decreased testicular weight)	Kaur and Parshad 1994 selenite
86	Rat (Fischer- 344)	13 wk (W)			^b 0.29 M (15% decreased sperm counts) 0.31 F (more time in diestrus and less time in proestrus, estrus, and metestrus than controls)		NTP 1994 selenate

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
87	Rat (Fischer- 344) (W)	13 wk		0.5 F	0.17 ^b M (11% decrease epididymal sperm counts) 0.86 F (more time in diestrus and less time in proestrus and estrus)		NTP 1994 selenite
88	Rat (Wistar)	12-14 wk ad lib				0.324 (testicular hypertrophy)	Turan et al. 1999a sodium selenite
89	Mouse (IVCS)	48 d ad lib (W)		0.17 F	0.34 F (proportion of mice with longer estrus cycles increased by 11.8%)		Nobunaga et al. 1979 selenite
90	Mouse (B6C3F1)	13 wk (W)		5.45 ^b M 7.17 F			NTP 1994 selenate
91	Mouse (B6C3F1)	13 wk (W)		3.31 ^b M 3.83 F			NTP 1994 selenite
92	Rabbit (New Zealand)	6 wks 1x/wk (GW)			0.001 M (significant reduction in serum testosterone (49%))		El-Zarkouny et al. 1999 sodium selenite
93	Pig (Duroc)	NS ad lib (F)				0.4 (decreased fertility, maternal toxicity)	Wahlstrom and Olson 1959b selenite

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Developmental							
94	Rat (Wistar)	8 wks ad lib (W)			0.64 (decrease weight gain of pups exposed during lactation)		Thorlacius-Ussing 1990 selenite
95	Mouse (IVCS)	pre-Gd:30 d Gd 0-18 ad lib (W)		0.17	0.34 (decreased fetal body weight; delayed vertebral ossification)		Nobunaga et al. 1979 selenite
96	Pig (Duroc)	NS ad lib (F)				0.4 (increased number of deaths between birth and weaning; reduced birth weight and reduced body weight at weaning)	Wahlstrom and Olson 1990 selenite
97	Cattle	3 mo ad lib (F)		0.265			Yaeger et al. 1998 sodium selenite
CHRONIC EXPOSURE							
Death							
98	Rat (Wistar)	2 yr ad lib (F)				0.5 (reduced longevity from about 500 days to about 60-100 days)	Harr et al. 1967; Tinsley 1967 selenate, selenite
Systemic							
99	Human	>3 yr (F)	Endocr	0.01 F			Bratton and Negretti De Bratton 1990 dietary

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
100	Human	>2 yr (F)	Hemato	0.0098			Longnecker et al. 1991 organic
			Musc/skel	0.0098			
			Hepatic	0.0098			
			Dermal	0.0098			
101	Human	Lifetime (F)	Dermal	0.015 ^c	0.023 (selenosis: sloughing of nails and brittle hair)		Yang and Zhou 1994 Organic
102	Human	yr (F)	Cardio	0.025			Yang et al. 1989a organic
			Hemato	0.015			
			Hepatic	0.025			
			Dermal	0.015			
103	Rat (Wistar)	2 yr ad lib (F)	Musc/skel	0.1	0.2 (soft bones)		Harr et al. 1967; Tinsley et al. 1967 selenite, selenate
			Hepatic	0.025	0.1 (hyperplastic lesions)		
			Renal	0.025	0.1 (nephritis)		

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
104	Rat (Osborne-Mendel)	24 mo ad lib (F)	Resp	0.5 F			Nelson et al. 1943 organic
			Gastro	0.5 F			
			Musc/skel	0.5 F			
			Hepatic			0.25 F (slight to moderate cirrhosis)	
			Endocr	0.5 F			
			Dermal	0.5 F			
105	Mouse (Swiss)	Lifetime ad lib (W)	Resp			0.57 (amyloidosis)	Schroeder and Mitchener 1972 selenate
			Cardio			0.57 (amyloidosis)	
			Hepatic			0.57 (amyloidosis)	
			Renal			0.57 (amyloidosis)	
			Endocr			0.57 (amyloidosis of adrenal gland)	
			Dermal		0.57 (poor coat)		
			Bd Wt	0.57			

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
106	Mouse (Swiss)	Lifetime ad lib (W)	Resp			0.57 (amyloidosis)	Schroeder and Mitchener 1972 selenite
			Cardio			0.57 (amyloidosis)	
			Hepatic			0.57 (amyloidosis)	
			Renal			0.57 (amyloidosis)	
			Endocr			0.57 (amyloidosis of adrenal gland)	
107	Human	yr (F)	Dermal		0.57 (poor coat)		
			Bd Wt	0.57			
				0.027		0.058 (tendon hyperflexia, peripheral anesthesia, pain in extremities, organic polyneuritis)	Yang et al. 1983
108	Rat (Wistar)	1 yr daily ad lib (W)		0.21	0.35 (50% reduction in number of pups reared in second generation)	1.05 (decreased fertility, pup survival, maternal toxicity; second generation failed to reproduce)	Rosenfeld and Beath 1954 selenate
109	Mouse (CD)	3 gen ad lib (W)				0.57 (failure to breed in the third generation)	Schroeder and Mitchener 1971b selenate

Table 3-2 Levels of Significant Exposure to Selenium - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	LOAEL			Reference Chemical Form
			System	NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
Developmental						
110	Mouse (CD)	3 gen ad lib (W)				0.57 (increased number of runts; postnatal lethality)
						Schroeder and Mitchener selenate

a The number corresponds to entries in Figure 3-2.

b Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive a chronic oral minimal risk level (MRL) of 0.005 mg/kg-day; The NOAEL is divided by an uncertainty factor of 3 (for human variability).

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; gastro = gastrointestinal; gd = gestation day; GHS-Px = selenium-dependent glutathione peroxidase; (GW) = gavage in water; Hemato = hematological; (IN) = ingestion; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; LPS = lipopolysaccharide; M = male; metab = metabolic; mg/kg/day = milligram per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; (W) = water; wk = week(s); x=time(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Selenium - Oral

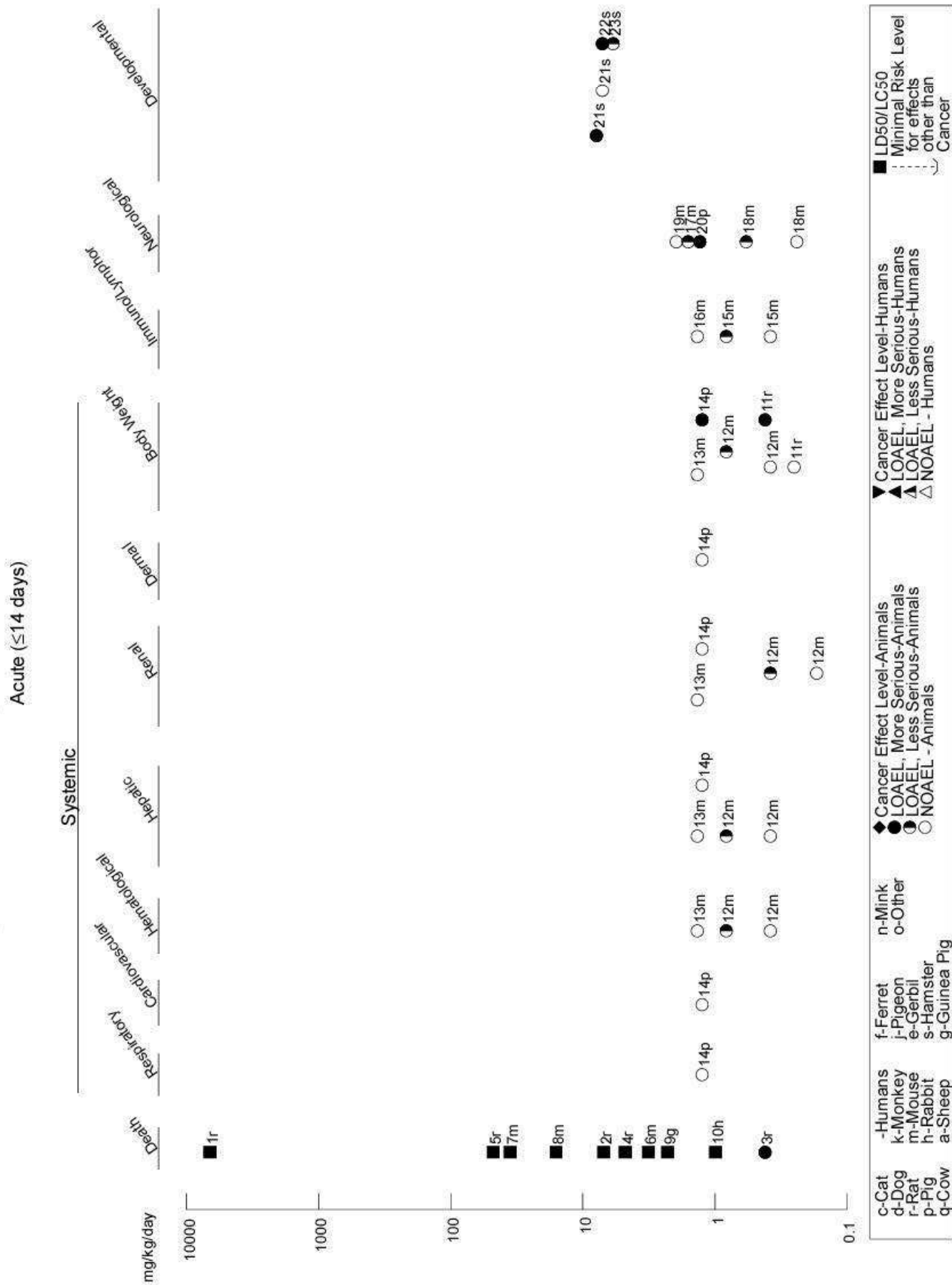
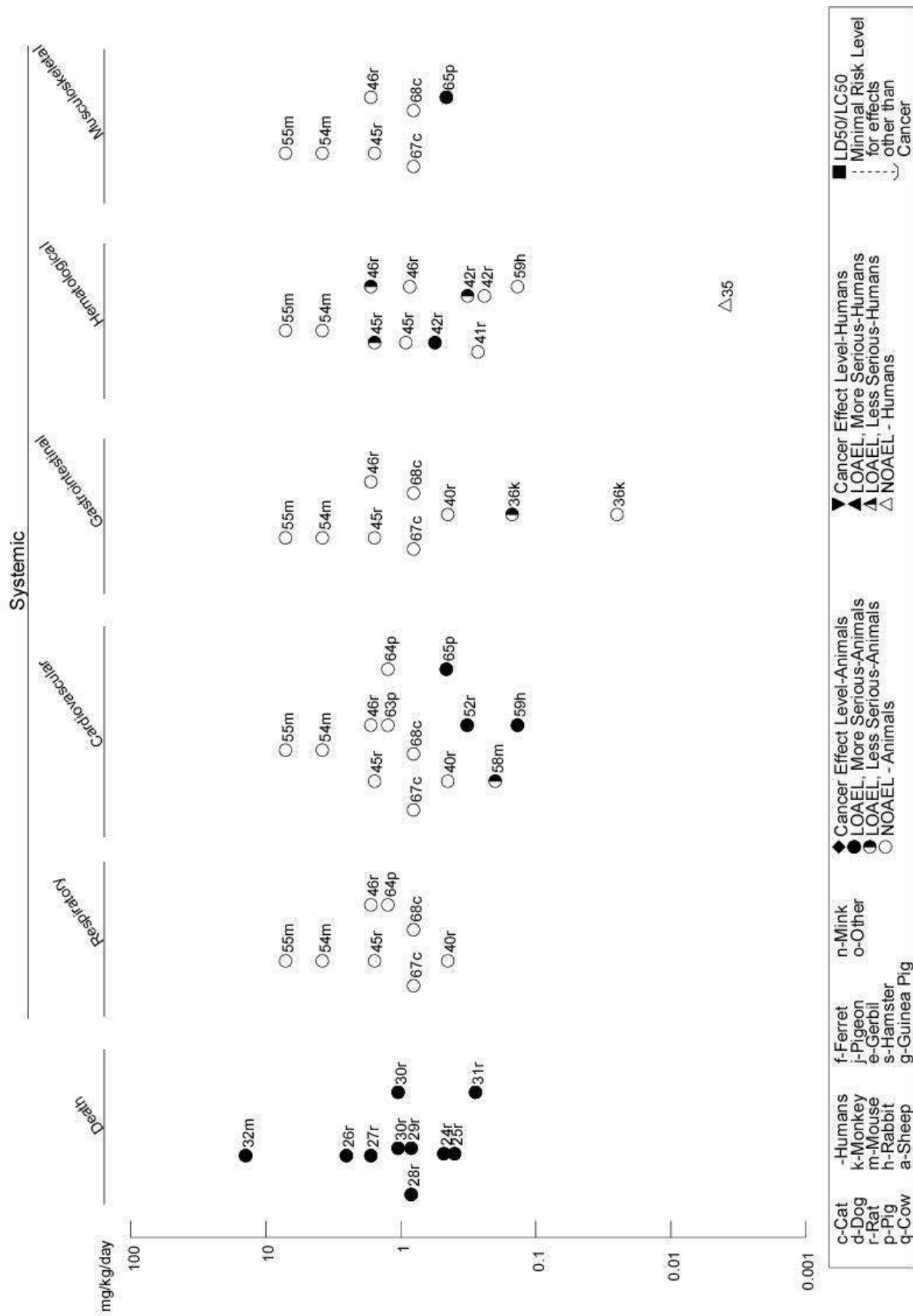


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (continued)



Intermediate (15-364 days)



Figure 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

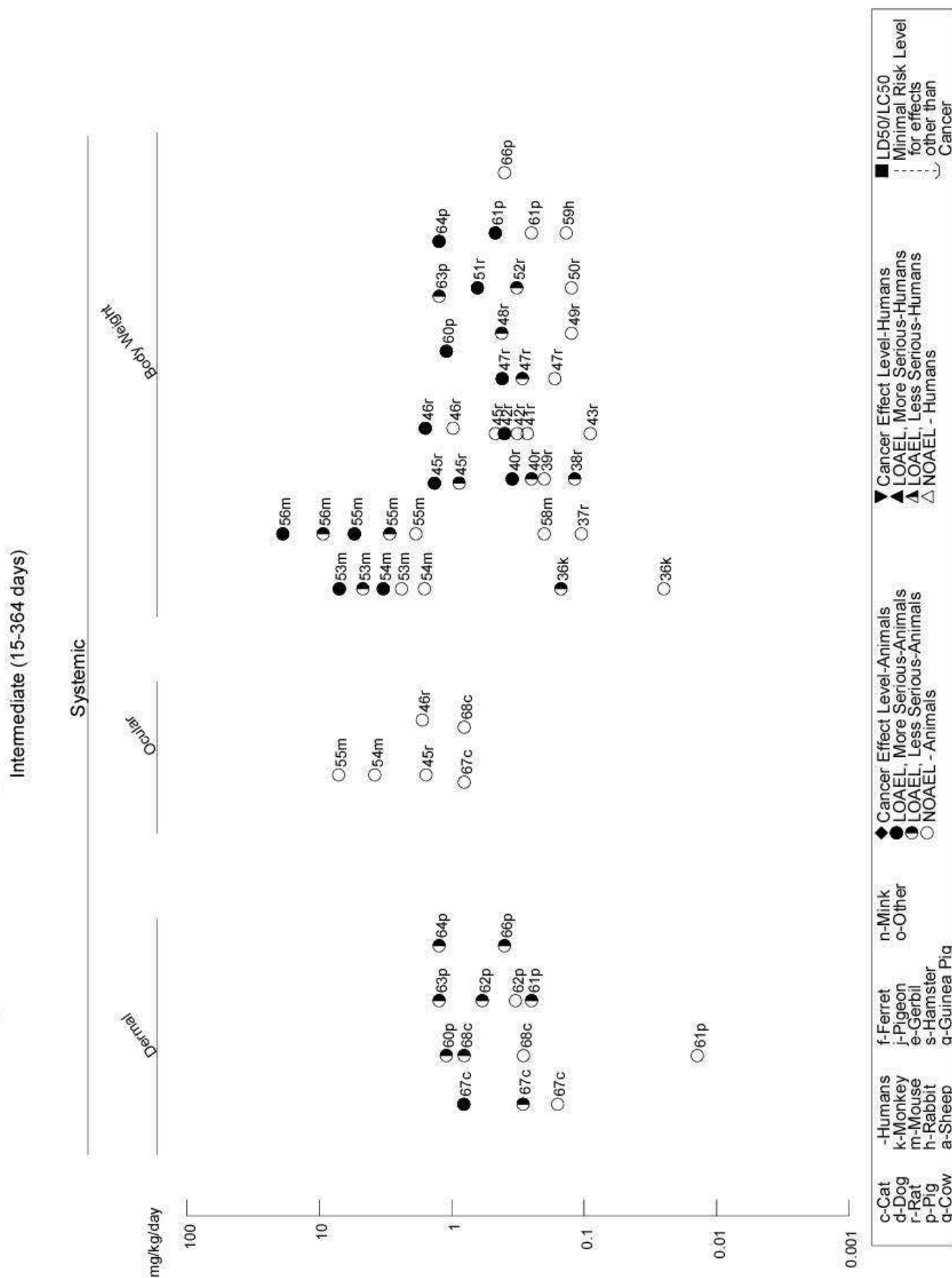


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

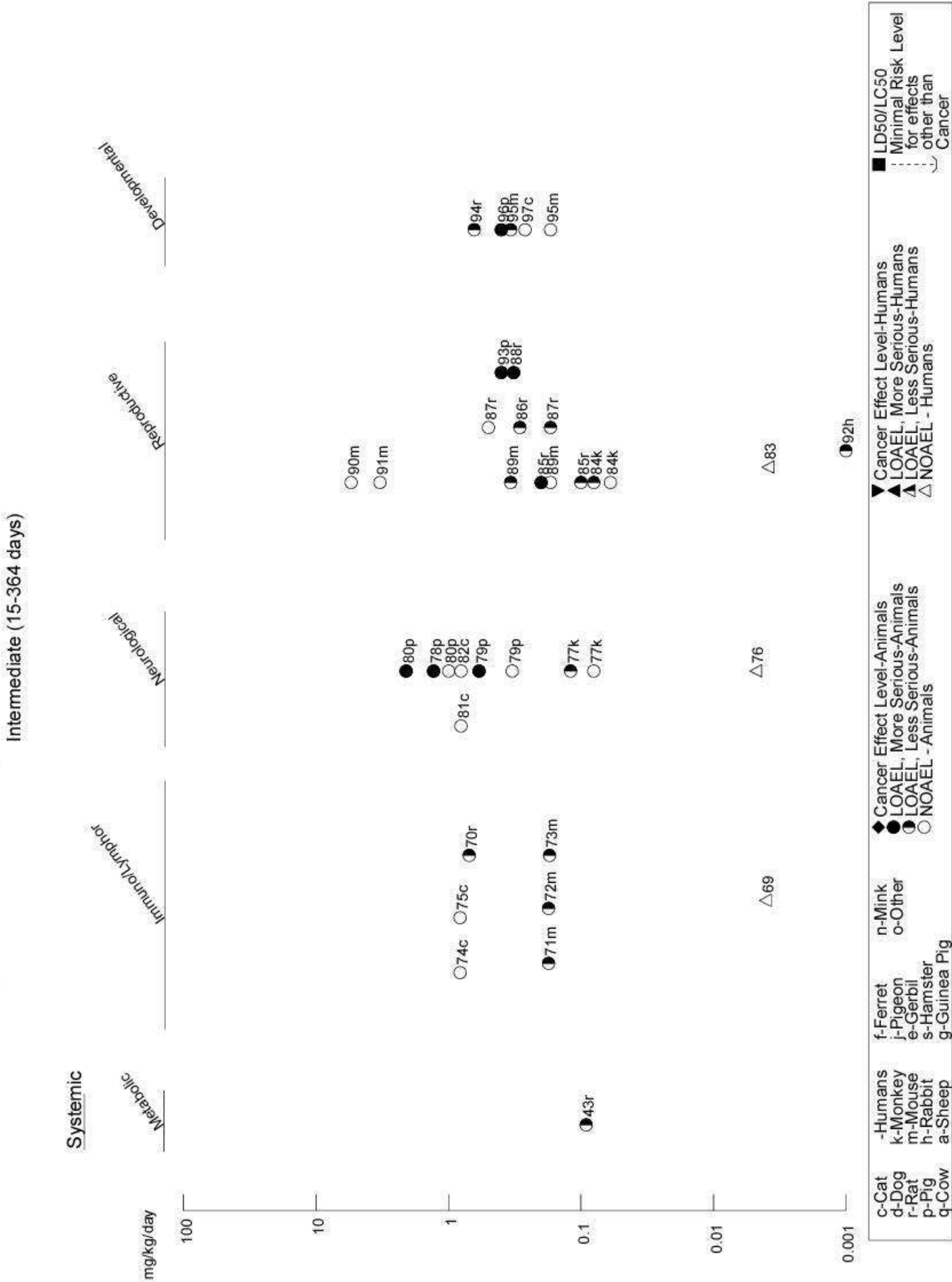


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

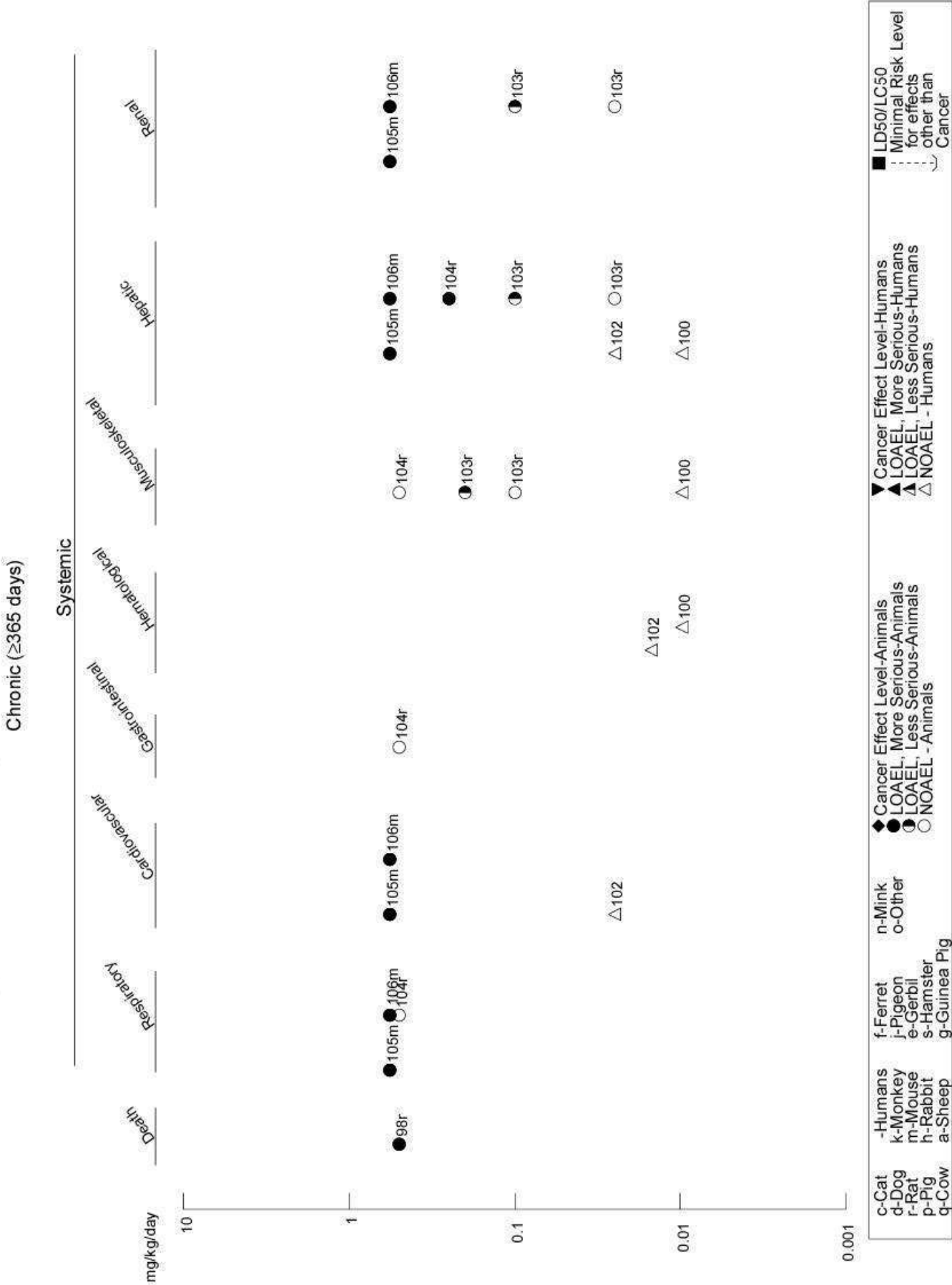


Figure 3-2. Levels of Significant Exposure to Selenium - Oral (continued)

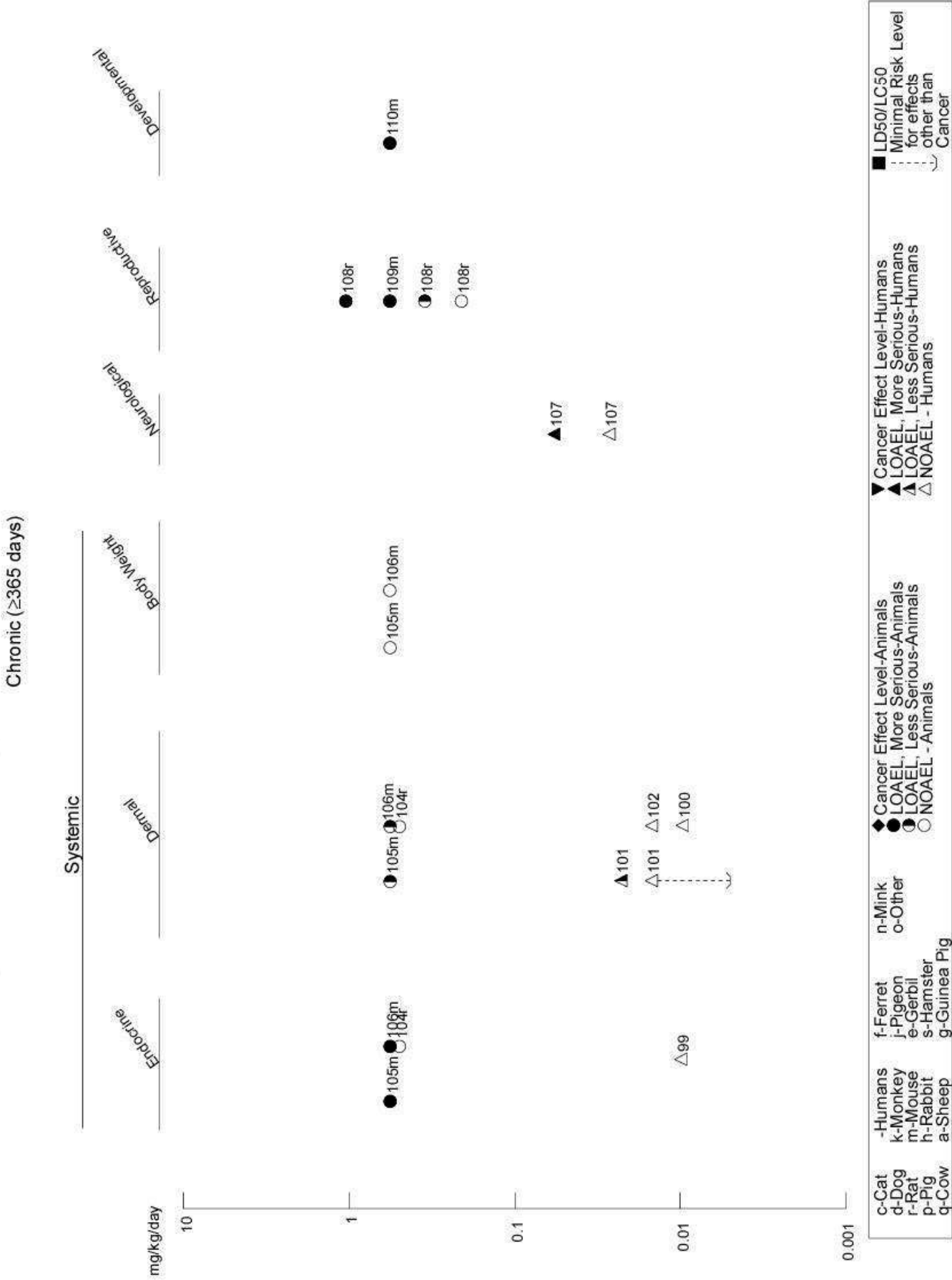


Table 3-3 Levels of Significant Exposure to Selenium Sulfides - Oral

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
1	Rat (Sprague-Dawley)	once (G)			138 M (LD50)	Cummins and Kimura 1971 SeS2 (aqueous)
2	Rat (Wistar)	once (GO)			75 M (3/6 died)	Moore et al. 1996b SeS
3	Rat (Wistar)	once (GO)			50 (3/15 died)	Moore et al. 1996b SeS
4	Mouse (NMRI)	once (G)			3700 (LD50)	Henschler and Kirschner 1969 SeS
5	Rat (Wistar)	once (GO)	Hepatic		75 M (widespread hepatic necrosis)	Moore et al. 1996b SeS
INTERMEDIATE EXPOSURE						
Death						
6	Rat (Fischer- 344)	17 d 1x/d (G)			112 M (LD50) 56 F ^b (LD50)	NTP 1980c SeS, SeS2
7	Mouse (B6C3F1)	17 d 1x/d (G)			805 M (LD50) 316 F ^b (LD50)	NTP 1980c SeS, SeS2

Table 3-3 Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Rat (Fischer- 344) 13 wk 7d/wk 1x/d (G)	Systemic	Resp	31.6			NTP 1980c SeS, SeS2
			Cardio	31.6			
			Gastro	31.6			
			Musc/skel	31.6			
			Hepatic	17.6	31.6 (focal necrosis)		
			Renal	31.6			
			Endocr	31.6			
			Dermal	31.6			
			Bd Wt	31.6			

Table 3-3 Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
9	Mouse (B6C3F1)	13 wk 7d/wk 1x/d (G)	Resp	464			NTP 1980c SeS, SeS2
			Cardio	464			
			Gastro	464			
			Musc/skel	464			
			Hepatic	464			
			Renal	216	464 (interstitial nephritis)		
			Endocr	464			
			Dermal	464			
			Bd Wt	216 F	464 F (body weight 17% lower than controls)		
CHRONIC EXPOSURE							
10	Rat (Fischer- 344)	103 wk 7d/wk 1x/d (G)					NTP 1980c
					15 (hepatocellular carcinomas 14/49 males, 21/50 females)		SeS, SeS2

Table 3-3 Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
11	Mouse (B6C3F1)	103 wk 7d/wk 1x/d (G)				100 F (hepatocellular carcinomas/adenomas 25/49, alveolar/bronchiolar carcinoma/adenomas 12/49)	NTP 1980c SeS, SeS2

a The number corresponds to entries in Figure 3-3.

b Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ab libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; gastro = gastrointestinal; (G) = gavage; gd = gestation day; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = time(s); yr = year(s)

Figure 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral

Acute (≤ 14 days)

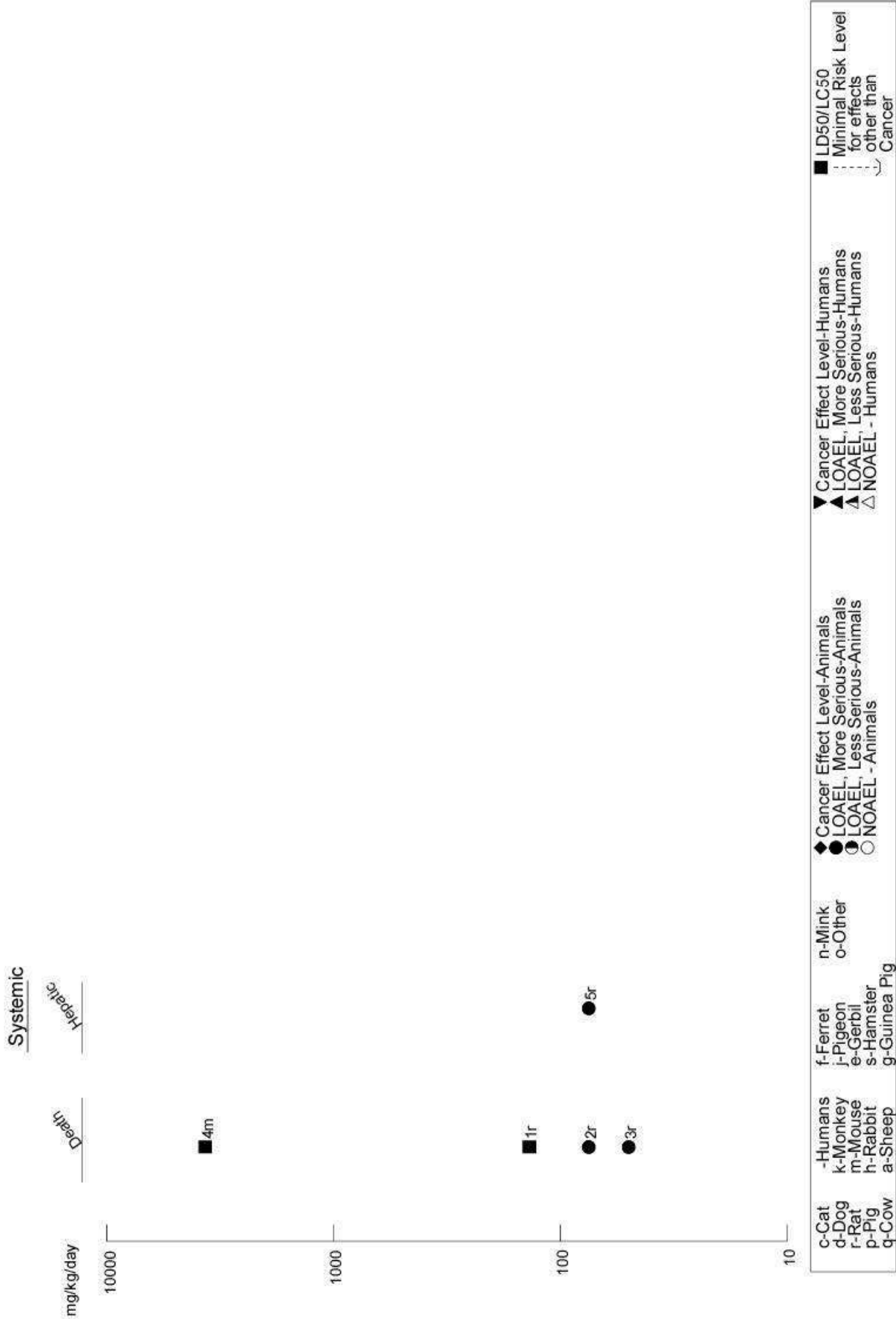


Figure 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral (continued)

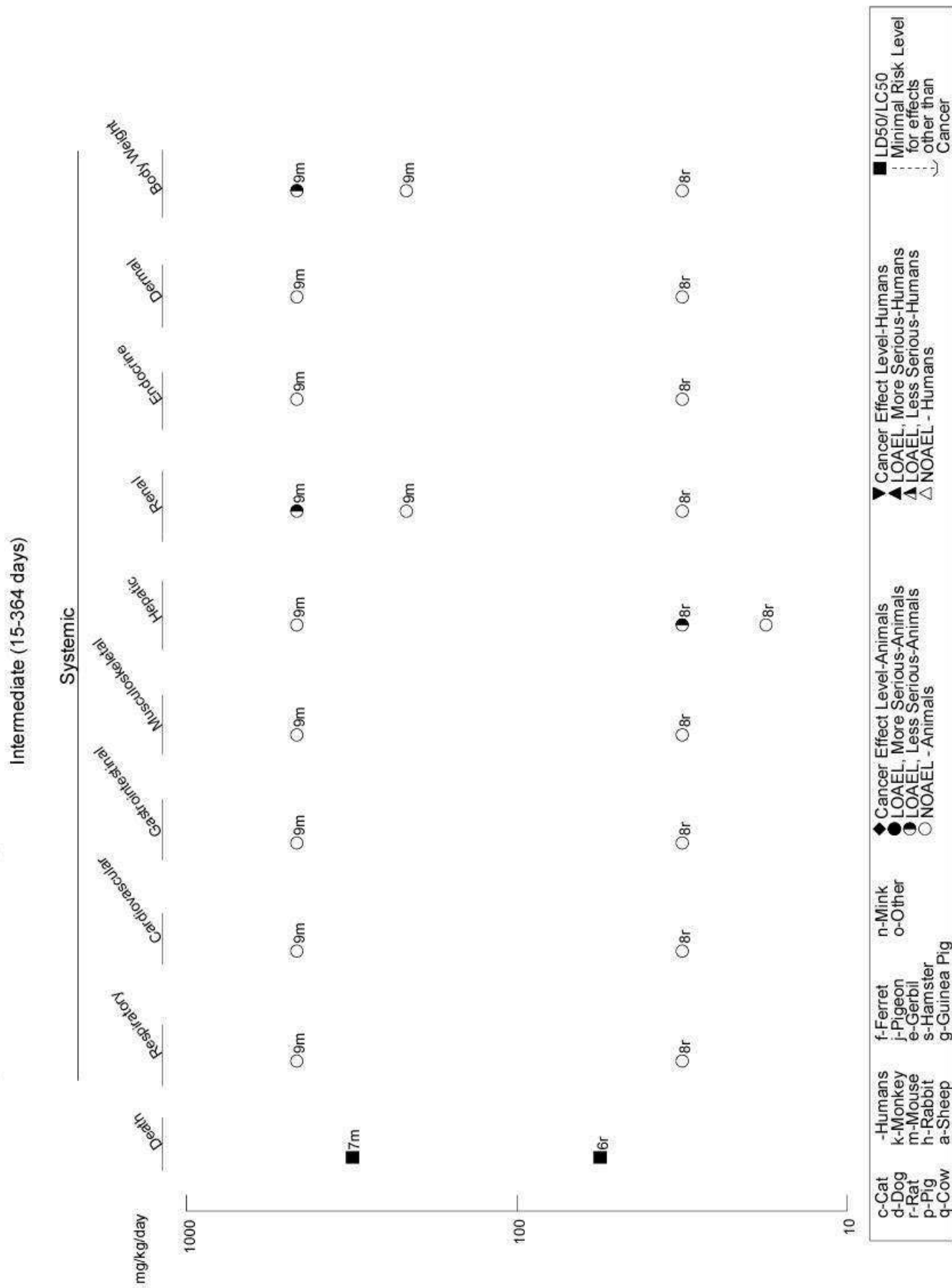
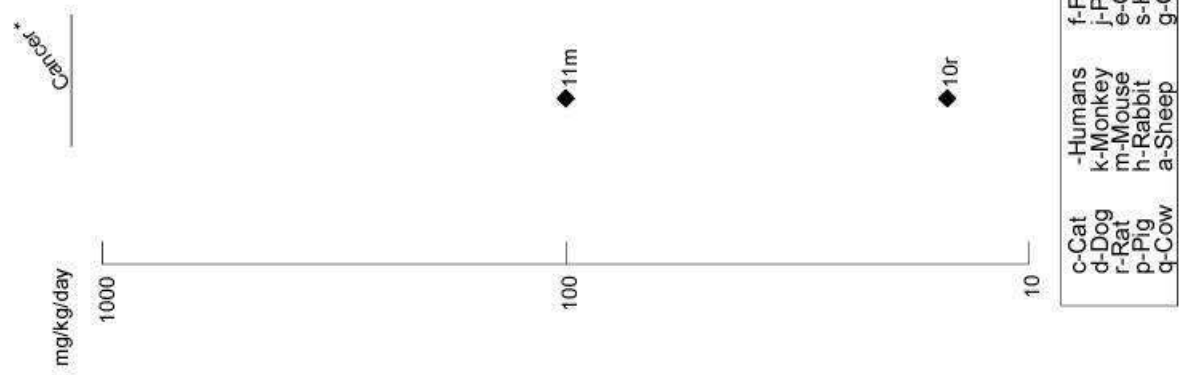


Figure 3-3. Levels of Significant Exposure to Selenium Sulfides - Oral (*continued*)

Chronic (≥ 365 days)



3. HEALTH EFFECTS

of the compound, because selenium sulfide preparations often exist as a variable mixture of the mono- and disulfide forms, precluding accurate expression of the dose in terms of total selenium.

Most of the available toxicity information for oral exposures to selenium compounds comes from domestic or experimental animal exposures to selenite, selenate, selenium sulfides (mixed), and organic selenium compounds (selenocystine, selenomethionine). Some of the earliest recognized effects of selenium were observed in livestock (cattle, sheep, and horses) that grazed on plants in areas of South Dakota, where soil selenium concentrations are naturally high. Selenium-associated effects observed in livestock include “blind staggers” and alkali disease. “Blind staggers” is an acute syndrome in which there is usually a slight impairment of vision, which can result in the animal straying from the herd. As the disease progresses, the blindness becomes more pronounced, and the animal may wander in circles. In the last stage, there are various degrees of paralysis and evidence of abdominal pain; death results from respiratory failure. However, because the effects have not been replicated in experimentally exposed cattle receiving doses of selenium sufficient to induce hoof lesions, the neurological signs associated with “blind staggers” may be due to compounds other than selenium in the vegetation. Alkali disease is a chronic disease in which the animals become emaciated, stiff, and lame; lose long hair from the mane and the tail; and the hooves become deformed. Alkali disease is also associated with atrophy of the heart and liver, while congestion and focal necrosis of the liver are more prominent in “blind staggers”.

Some epidemiological studies report data from populations exposed to selenium in the food chain in areas with high selenium levels in soil. It is likely that selenite, selenate, and the selenium found in food and in dietary supplements comprise the majority of selenium compounds to which oral, off-site selenium exposures will occur at or near hazardous waste sites. Aside from the variation in effective dose, the health effects from exposure to selenate, selenite, and dietary selenium are not expected to differ greatly. However, oral exposures to many other compounds of selenium could occur (primarily through soil or edible plant ingestion) if those compounds were deposited at the site, or if local environmental conditions greatly favor transformation to those forms. Heavy metal selenides, aluminum selenide, tungsten diselenides, and cadmium selenide are used in industry and may end up in waste sites. Mobilization of selenium, typically as selenate in water run-off, has the potential to impact nearby plants and animals, thus potentially exposing people through eating game meat, local plants, and agricultural or livestock food products from the area.

3.2.2.1 Death

Accidental selenium poisonings in humans have occurred, but few fatalities have been reported. The selenium doses associated with the reported deaths are unknown (Carter 1966; Koppel et al. 1986). One 3-year-old boy died 1.5 hours after ingestion of an unknown quantity of selenious acid contained in a gun-bluing preparation (Carter 1966). Clinical signs included excessive salivation, garlic odor on the breath, and shallow breathing. A 15-year-old female survived ingestion of a solution of sodium selenate estimated to have provided 22 mg selenium/kg body weight, probably because she was forced to vomit soon after exposure (Civil and McDonald 1978). Clinical signs included garlic odor of the breath and diarrhea.

No cases of human death in the United States have been attributed to intermediate or chronic oral exposures to selenium or selenium compounds. In the Hubei Province of China, in an area of endemic selenosis, a woman who died was suffering from hemiplegia thought to have been caused by chronic selenosis induced by eating locally grown foods that contained high levels of organic selenium compounds (Yang et al. 1983). However, an autopsy was not performed and no clinical history of previous illness was available.

In nonhuman animals, the most acutely toxic selenium compounds by ingestion appear to be sodium selenite and sodium selenate (Olson 1986). Oral LD₅₀ values for sodium selenite, expressed as mg selenium/kg body weight, were reported as 4.8–7.0 in rats, 1.0 in rabbits, 3.2 in mice, and 2.3 in guinea pigs (Cummins and Kimura 1971; Pletnikova 1970). Minimum lethal doses of sodium selenite, expressed as mg selenium/kg body weight, reported for larger animals were 13–18 for pigs and 9.9–11.0 for cows (Miller and Williams 1940); however, these values were estimated on the basis of a small number of animals. Two of four 12-week-old lambs died within 16 hours of administration of 5 mg selenium/kg as sodium selenite (Smyth et al. 1990). Selenium dioxide is reported to have LD₅₀ values of 16 mg selenium/kg for mice and 48 mg selenium/kg body weight for rats, but these values are also based on a small number of animals (Singh and Junnarkar 1991). An oral LD₅₀ of 35.9 mg selenium/kg has been reported for L-selenocystine given to mice (Sayato et al. 1993). Elemental selenium is less toxic than most selenium compounds, because of its extremely low solubility; an LD₅₀ of 6,700 mg selenium/kg body weight has been reported for oral administration of elemental selenium as a suspension (particle size 1–30 µm) in 0.5% methylcellulose to rats (Cummins and Kumura 1971).

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Lower doses of selenium can cause signs of toxicity if administered over extended periods of time. Eight weaned 5-week-old pigs receiving 1.3 mg selenium/kg/day as sodium selenite in gelatin capsules daily for 10 days died during one study; only one dose level was tested (Wilson et al. 1989). Two long-tailed macaques administered 0.60 mg selenium/kg/day as selenomethionine by nasogastric intubation died of either anorexia or aspirated vomitus secondary to emesis and gastritis after 10 or 15 days of treatment (Cukerski et al. 1989). Seven of 12 female rats receiving diets containing 0.418 mg selenium/kg/day as sodium selenate for 14 days died before the end of the experiment (NTP 1996). Exposure to selenium in drinking water at a level of 0.84 mg selenium/kg/day as selenite or selenate for 4–6 weeks resulted in the death of four of six or two of six male rats, respectively (Palmer and Olson 1974). Feeding male rats diets containing 0.48 mg selenium/kg/day as sodium selenite or 0.4 mg selenium/kg/day as seleniferous wheat for 6 weeks resulted in the death of one of eight rats in each group (Halverson et al. 1966). Administration of sodium selenite in drinking water at a level of 0.28 mg selenium/kg/day for 58 days resulted in the death of 25 of 50 male rats (Schroeder and Mitchener 1971a). Mortality was observed in rats, but not in mice, receiving either 1.67 mg selenium/kg/day as sodium selenite or 2.54 mg selenium/kg/day as sodium selenate in drinking water for 13 weeks (NTP 1994). Gavage treatment of male mice with selenocystine 6 days per week for 30 days at a dose of 14.2 mg selenium/kg killed all 15 treated animals, while no deaths were noted at 9.4 mg selenium/kg (Sayato et al. 1993). The longevity of hamsters was not affected by dietary administration of sodium selenite at a dose of 0.42 mg selenium/kg/day for 124–144 weeks (Birt et al. 1986).

Sodium selenate and sodium selenite exhibit similar toxicity in female rats, but male rats appear more susceptible to the toxicity of sodium selenite than selenate (Palmer and Olson 1974; Schroeder and Mitchener 1971a). Sodium selenate in drinking water at 0.28 selenium mg/kg/day for 1 year did not increase mortality of male or female rats compared with control rats (Schroeder and Mitchener 1971a). Ingestion of 0.28 mg selenium/kg/day of sodium selenite in drinking water for 1 year did not increase mortality in female rats, whereas 50% of the males died by day 58 of administration (Schroeder and Mitchener 1971a).

The relative acute toxicities of sodium selenite, potassium selenite, sodium selenate, and potassium selenate in aqueous solution have been examined in mice (Pletnikova 1970). No significant differences among the toxicities of the potassium and sodium salts of selenium were apparent in this study. In another study, rats tolerated a dose of 1.05 mg selenium/kg/day administered in drinking water as potassium selenate for over 8 months with no deaths, but three of five females and one of three males died by the end of 1 year (Rosenfeld and Beath 1954). Decreased survival was reported in rats fed sodium

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selenate or selenite at 0.5 mg selenium/kg/day in a 2-year cancer study (Harr et al. 1967; Tinsley et al. 1967). No mortality was observed in hamsters fed 0.42 mg selenium/kg/day as sodium selenite in the diet for 82–142 weeks (Birt et al. 1986).

Selenium sulfide (i.e., selenium monosulfide) and selenium disulfide are less water soluble and are of lower acute toxicity than sodium selenate or sodium selenite. There are no reported human deaths due to ingestion of selenium sulfide. The LD₅₀ value for the gavage administration of 1–20% selenium disulfide in aqueous 0.5% methylcellulose to rats was 138 mg selenium disulfide/kg (Cummins and Kimura 1971). When 1% selenium disulfide shampoo was administered by gavage, the LD₅₀ value was lower (78 mg selenium disulfide/kg) (Cummins and Kimura 1971). The compound administered may have been a mixture of selenium sulfide and selenium disulfide; analysis of the compound was not reported. Henschler and Kirschner (1969) reported an LD₅₀ of 3,700 mg selenium sulfide/kg for mice administered by gavage in aqueous 0.5% carboxymethylcellulose. Administration of single gavage doses of selenium monosulfide to rats produced death in 3/15 animals dosed with 50 mg/kg, 3/6 animals dosed with 75 mg/kg, 1/2 animals dosed with 100 mg/kg, and 2/2 animals dosed with 125 mg/kg (Moore et al. 1996b).

In the case of selenium sulfide, mice are more tolerant than rats, and males of both species appear to be more tolerant than females (NTP 1980c). The daily doses producing 50% mortality for a 17-day gavage administration of a mixture of selenium mono- and disulfides were 112 mg selenium sulfides/kg for male rats, 56 mg selenium sulfides/kg for female rats, and 805 mg selenium sulfides/kg for male mice (NTP 1980c). A 13-week gavage study using the same mixture of selenium mono- and disulfides reported survival as 10/10, 10/10, 10/10, 9/9, 8/9, and 6/10 in female mice and 10/10, 10/10, 10/10, 10/10, 10/10, and 9/10 in male mice receiving 0, 21.6, 46.4, 100, 216, and 464 mg selenium sulfides/kg/day, respectively (NTP 1980c). Although the researchers intended to administer selenium monosulfide to the animals, elemental analysis, melting point, and x-ray diffraction revealed that the compound administered included some selenium disulfide. No other chemical or physical analyses of the selenium compound administered were reported.

The LD₅₀ and lethal LOAEL values from each reliable study following oral exposure to elemental selenium dust, selenium dioxide dissolved in water (selenious acid), sodium selenate, sodium selenite, potassium selenate, and dietary selenium for each species and exposure duration are recorded in Table 3-2 and plotted in Figure 3-2. The LOAEL values for death in rats and mice following acute and intermediate

oral exposures to selenium sulfide or selenium disulfide are recorded in Table 3-3 and plotted in Figure 3-3.

3.2.2.2 Systemic Effects

The highest NOAEL value and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Respiratory Effects. Pulmonary edema and lesions of the lung have been noted in case reports of humans (Carter 1966; Koppel et al. 1986) and animals (Glenn et al. 1964a; Rosenfeld and Beath 1947) after ingestion of lethal doses of selenium compounds. Rabbits orally administered sodium selenite (subroute not specified) at levels approximating the LD₅₀ (1–5 mg selenium/kg body weight) developed pulmonary congestion, hemorrhages, and edema; dyspnea; general muscular weakness; and asphyxial convulsions (Smith and Westfall 1937). Pulmonary edema and hemorrhages were observed in four sheep treated orally (subroute not specified) with a single dose of sodium selenite of 5 mg selenium/kg (Smyth et al. 1990). The lungs may be a target of acute exposure to excess selenium because the metabolite, dimethyl selenide, is exhaled.

The effects of intermediate or chronic exposures to selenium compounds are less clear. Although Harr et al. (1967) stated that absolute lung weights decreased with increasing doses of selenite or selenate chronically administered to rats in the diet in a 2-year cancer study, they did not report lung weights at specific dose levels. Selenium administration also might have contributed to pneumonic lesions, but again, the authors did not statistically analyze their results or relate the severity of the effect to the doses of selenium administered. Respiratory effects were not observed in rats treated with selenite in the diet for 8 weeks at a dose of 0.45 mg selenium/kg/day (Chen et al. 1993). Effects on the lungs were not observed in pigs fed 1.25 mg selenium/kg as organic selenium found in the plant *Astragalus bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate in the diet for up to 6 weeks (Panter et al. 1996). Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any signs of respiratory distress or changes in lung weight or histology (O'Toole and Raisbeck 1995). Ingestion of selenium in drinking water for 13 weeks at doses up to 1.67 and 7.17 mg selenium/kg as selenate in rats and mice, respectively, and 1.57 and 3.83 mg selenium/kg as selenite in rats and mice, respectively, did not cause any respiratory effects (NTP 1994). Nelson et al. (1943) reported that no effects on the lungs were apparent in rats administered 0.50 mg selenium/kg/day as seleniferous corn for 2 years.

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An increased incidence of amyloidosis of the major organs, including the lungs, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p < 0.001$) of selenium-treated mice. Data for individual organs were not provided.

Administration of lethal doses of selenium sulfide particles in carboxymethylcellulose by gavage has been reported to cause irregular breathing in mice (Henschler and Kerschner 1969), but not in rats (Cummins and Kimura 1971). No respiratory effects were seen in mice administered 464 mg selenium sulfides/kg/day or in rats administered 31.6 mg selenium sulfides/kg/day by gavage once daily for 13 weeks (NTP 1980c).

Cardiovascular Effects. Tachycardia has occasionally been reported as a result of a lethal, acute oral exposure to selenium compounds in humans (Carter 1966); however, the dose was not reported in this lethal exposure to a gun-bluing solution containing selenious acid. Although myocardial disorders (cardiogenic shock, congestive heart failure, arrhythmia, multifocal necrosis of the myocardium) have been associated with selenium deficiencies (Yang et al. 1988), none has been reported to be associated with chronic dietary selenosis in humans observed at doses of ≥ 0.016 mg/kg/day (Yang et al. 1989a). A preliminary study completed in China suggests that selenium supplementation (100 μ g/day, form not stated) during pregnancy may reduce the incidence of pregnancy-induced hypertension (Li and Shi-mei 1994).

In contrast, postmortem studies of sheep that died from acute oral exposure to sodium selenite or sodium selenate have revealed petechial hemorrhages of the endocardium (Glenn et al. 1964a; Smyth et al. 1990). The sheep were treated with a time-weighted average dose of 0.65 or 0.9 mg selenium/kg/day as selenate over a 171-day period (Glenn et al. 1964a, 1964b), or a single dose of selenite at 5 mg selenium/kg (Smyth et al. 1990). Vacuolation and pyknosis of nuclei were observed in the hearts of pigs fed an unspecified form of selenium at a dose of 0.46 mg selenium/kg/day for 34 days (Stowe et al. 1992). In a 2-year cancer study, Harr et al. (1967) reported the occurrence of myocardial hyperemia, hemorrhage, and degeneration, as well as pericardial edema, in young rats administered sodium selenite or sodium selenate in the feed at doses of 0.5 mg selenium/kg/day, although the authors did not specify the duration of exposure required to produce the effects.

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Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several of the animals (Penrith and Robinson 1996). Histological examination of heart tissue from pigs that died revealed myocardial lesions consisting of widespread hypertrophy, atrophy, and disorganization of fibers, occasional fibrosis, and marked medial hypertrophy of the arterioles.

Wistar rats administered 0.324 mg selenium/kg/day as sodium selenite in food for 12–14 weeks showed severe diffuse degenerative changes, including edema in the sub-endocardial connective tissue and the interfibers of prevascular regions, and myofibril swelling with profuse intercellular edema (Turan et al. 1999a). Myocyte borders were irregular, and there was a loss of striations and a degeneration of the sarcolemma and myofibril structure and order. Examination of the mechanical function of the heart *in vitro* using either Langendorff perfusion or papillary muscle recordings showed increased coronary perfusion pressure, increased resting force, and increased heart rate with irregular beating. No difference in contractile force was observed. Chronic heart failure did not occur in any of the animals in the study.

Cardiac damage was also observed in mice exposed to 0.2 mg selenium/kg/day as sodium selenite in food for 12 weeks (Skowerski et al. 1997b). Ultrastructural examination revealed cardiomyocytes that had numerous damaged mitochondria, a large number of lipid droplets, and numerous lysosomes.

Hearts of New Zealand white rabbits administered 0.137 mg selenium/kg/day as sodium selenite in food for 3 months showed distinct, degenerative changes indicating disintegration of the internal structure of the myocytes (Turan et al. 1999b). Muscle fibers were fragmented and separated. Disruption and loss of myofibrils was observed, sarcomeres were irregular, and the I, Z, and H bands were disorganized and discontinuous. Mitochondria were fewer and more variable in size and shape, with disoriented cristae and a loss of matrix substance. Hearts of control animals (0.007 mg selenium/kg/day) had normal histology.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in heart weight or histology (O'Toole and Raisbeck 1995). Histopathological changes in the heart were not observed in pigs fed selenium at 1.25 mg selenium/kg as organic selenium found in the plant *A. bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate for up to 6 weeks (Panter et al. 1996). Histopathological changes were not observed in the hearts of rats treated with selenite in the diet for 8 weeks at a dose of 0.45 mg selenium/kg/day (Chen et al. 1993). Selenium administered to rats and mice in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate, respectively, and up to 1.67 and 3.83 mg selenium/kg/day as selenite, respectively, did not cause any histopathological changes in the heart tissue (NTP 1994). No

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histopathological changes were noted in mice administered 464 mg selenium sulfides/kg/day or in rats administered 31.6 mg selenium sulfides/kg/day by gavage once daily for 13 weeks (NTP 1980c).

An increased incidence of amyloidosis of the major organs, including the heart, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p < 0.001$) of selenium-treated mice. Data for individual organs were not provided.

Although myocardial degeneration and necrosis have been experimentally induced in laboratory animals and livestock including cattle, sheep, and swine by acute and longer-term exposures to inorganic salts of selenium, it is unclear whether seleniferous grains or forages, or other natural sources of selenium, can also cause cardiomyopathy (Raisbeck 2000).

Gastrointestinal Effects. In humans, gastrointestinal distress, including nausea, vomiting, diarrhea, and abdominal pain, has been reported following ingestion of aqueous sodium selenate (Civil and McDonald 1978; Gasmi et al. 1997; Helzlsouer et al. 1985; Koppel et al. 1986; Sioris et al. 1980). Two studies provided an estimate of dose. In a case report by Civil and McDonald (1978), diarrhea was observed in a 15-year-old girl about 45 minutes after she swallowed sheep drench containing selenate at a dose of about 22 mg selenium/kg. This effect was observed despite the induction of vomiting shortly after the exposure. In a second case report of a suicide attempt, a 56-year-old man reported that vomiting, diarrhea, and abdominal pain occurred 1 hour after he ingested approximately 11 mg/kg selenium as sodium selenite (Gasmi et al. 1997). Postmortem examinations following two deaths from selenium ingestion revealed dilation of the stomach and small intestine (Carter 1966) and erosive changes of the gastrointestinal tract (Koppel et al. 1986). High (unspecified) levels of dietary selenium compounds have been implicated as causing gastrointestinal disturbances in chronically exposed humans (Smith et al. 1936), but such symptoms are not specific to selenium intoxication.

Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several animals. Clinical signs included anorexia and vomiting, and histological examination (70–79 days after exposure) of three of the exposed animals that died found lesions ranging from small erosions (1–2 mm diameter) to extensive mucosal necrosis (up to 100 mm diameter) near the cardia of the stomach (Penrith and Robinson 1996).

Gross necropsy of steers that died after ingestion of sodium selenite revealed severe gastrointestinal irritation (Baker et al. 1989; Maag et al. 1960). In addition, cattle and other livestock exhibiting alkali

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disease, perhaps as a result of long-term consumption of range plants high in selenium, ate and drank less and suffered from ulcers in the upper intestinal tract (Shamberger 1986). A single oral dose of 5 mg selenium/kg as selenite caused edema and congestion of abdominal viscera in lambs (Smyth et al. 1990). However, treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in histology of the gastrointestinal tissues (O'Toole and Raisbeck 1995).

Gastrointestinal effects were not observed in rats treated with selenite in the diet for 8 weeks at a dose of 0.45 mg selenium/kg/day (Chen et al. 1993). Selenium treatment in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate in rats and mice, respectively, and 1.67 and 3.83 mg selenium/kg/day as selenite in rats and mice, respectively, did not cause any gastrointestinal effects (NTP 1994). Gastrointestinal effects were not observed in rats fed organic selenium (seleniferous corn or wheat) at 0.5 mg selenium/kg/day for 24 months (Nelson et al. 1943). Vomiting and anorexia were reported in monkeys receiving 0.15 mg/kg/day selenium as L-selenomethionine by oral intubation during gestation days 20–50 (Tarantal et al. 1991).

Selenium sulfide administration by gavage at lethal levels has been reported to cause diarrhea and anorexia in rats (Cummins and Kimura 1971). No gastrointestinal effects were seen in mice administered 464 mg selenium sulfide/kg/day or in rats administered 31.6 mg selenium sulfide/kg/day by gavage once daily for 13 weeks (NTP 1980c).

Hematological Effects. Hematological changes were evaluated in a 120-day double blind study of healthy men who consumed a controlled diet of foods naturally low or high in selenium (Hawkes et al. 2001). Eleven subjects were fed 0.0006 mg selenium/kg/day in the diet for 21 days (baseline period), followed by 0.0002 mg/kg/day (6 subjects) or 0.004 mg/kg/day (5 subjects) for the following 99 days. Complete blood counts (white blood cells, lymphocytes, granulocytes, platelets, erythrocytes, hematocrit) and hemoglobin concentration measurements showed no adverse effects of selenium supplementation. Mean within-subject changes from baseline in white blood cell counts were significantly different in the low- and high-selenium groups at last two time points in the study (days 70 and 99). At the end of the study, the white blood cell counts were decreased by 5% in the high-selenium group and increased by 10% in the low-selenium group, due mainly to changes in numbers of granulocytes. Lymphocyte counts were significantly increased in the high-selenium group on day 45, but not at the end of the study. There were no clear effects of selenium on numbers of activated or cytotoxic T-cells, lymphocyte phenotypes,

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serum immunoglobulins, or complement fractions, as summarized in Section 3.2.2.3 (Immunological Effects).

Increased prothrombin time was reported for individuals chronically exposed to estimated dietary doses of 0.016 mg selenium/kg/day in a high-selenium region of China (Yang et al. 1989a). However, no increase in prothrombin time was found in another study of individuals consuming diets that supplied up to 0.0098 mg/kg/day selenium (Longnecker et al. 1991). A study that compared children from seleniferous and nonseleniferous areas of Venezuela found slightly reduced (no statistical analysis was performed) hemoglobin levels and hematocrit values for the children from the seleniferous area (Jaffe et al. 1972). However, the children from the seleniferous zone had a poorer diet, consumed less milk and meat, and had a greater incidence of intestinal parasites, which may account for the differences observed. Red blood cell counts were significantly increased in mice that received drinking water containing 9 ppm (0.82 mg selenium/kg/day) selenium as sodium selenite for 14 days (Johnson et al. 2000). However, these mice also had a severe reduction in water consumption (43%) and this may have led to a decrease in blood volume. No significant increase in red blood cell count (or decrease in water consumption) was observed for mice receiving 3 ppm (0.38 mg selenium/kg/day) selenium as sodium selenite, or up to 9 ppm (1.36 mg selenium/kg/day) selenium as selenomethionine for 14 days (Johnson et al. 2000).

No hematological changes (hemoglobin concentration, hematocrit, erythrocyte count, and cell volume) were reported for male Sprague-Dawley rats fed diets providing up to 0.27 mg selenium/kg/day as sodium selenite for 40 days (Eder et al. 1995). Increased hematocrit was observed in rats treated with selenate (1.56 mg selenium/kg/day) or selenite (1.67 mg selenium/kg/day) in the drinking water for 13 weeks, but only at concentrations that decreased water intake (NTP 1994). No effects on hematology end points were observed in mice treated with selenate or selenite in drinking water for 13 weeks at 7.17 mg selenium/kg for selenate and 3.83 mg selenium/kg/day for selenite (NTP 1994).

No differences in blood cell counts or hematological parameters were found in rabbits administered 0.137 mg selenium/kg/day as sodium selenite in the diet for 3 months, compared with control animals receiving a normal laboratory diet (Turan et al. 1999b).

A dose-related decrease in hematocrit was observed in rats fed seleniferous wheat (Halverson et al. 1966). Compared to controls, hemoglobin was decreased 23 and 79% at 0.32 and 0.56 mg selenium/kg/day, respectively. Hemoglobin reductions were most evident in the animals that had died during the experiments. In a 2-year cancer study, Harr et al. (1967) reported that the hemoglobin concentration

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decreased by 0.5 g/100 mL with each 2-fold increase of sodium selenate in the diet, but did not specify the lowest dose at which hemoglobin concentrations were significantly reduced compared to the controls (the range of selenium doses used was 0.025–0.40 mg selenium/kg/day). Hematocrit was increased in rats given selenite and selenate in drinking water for 13 weeks at concentrations that also resulted in decreased water intake (NTP 1994). No hematological effects were noted in rats or mice treated with selenate at 0.92 and 7.17 mg selenium/kg/day, respectively, or selenite at 0.86 and 3.83 mg selenium/kg/day, respectively (NTP 1994).

No studies were located regarding hematological effects in humans or other animals after oral exposure to selenium sulfide or selenium disulfide.

Musculoskeletal Effects. No adverse musculoskeletal effects were reported following chronic oral exposure of humans to dietary levels of selenium of up to 0.0098 mg selenium/kg/day (Longnecker et al. 1991).

A single oral (subroute not specified) dose of sodium selenite (5 mg selenium/kg/day) caused edema in skeletal muscles of the diaphragm in sheep (Smyth et al. 1990). Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several animals (Penrith and Robinson 1996). Histological examination of skeletal muscle from animals that died found damage with interstitial oedema and diffuse swelling of fibers. Livestock suffering from chronic alkali disease, a disease once common in the southwestern United States where selenium levels are high, showed lameness due to joint erosion and hoof deformation (Shamberger 1986). However, treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in muscle or bone histology (O'Toole and Raisbeck 1995). Hyperplasia of the sarcolemma nuclei and disintegration of myofibrils were observed in the skeletal muscles of pigs fed an unspecified form of selenium for 34 days (Stowe et al. 1992). In a 2-year cancer study, Harr et al. (1967) fed graded doses of selenium in the form of sodium selenate or selenite to rats and reported frank osteotoxicity at doses as low as 0.2 mg selenium/kg/day given for several months (duration specified as less than 100 days). Selenium administered in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate in rats and mice, respectively, and 1.67 and 3.83 mg selenium/kg as selenite in rats and mice, respectively, failed to cause adverse musculoskeletal effects (NTP 1994). Musculoskeletal effects were not observed in rats fed seleniferous corn or wheat at 0.5 mg selenium/kg/day for 24 months (Nelson et al. 1943). No musculoskeletal effects were seen in mice

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administered 464 mg selenium sulfide/kg/day or in rats administered 31.6 mg selenium sulfide/kg/day by gavage once daily for 13 weeks (NTP 1980c).

Hepatic Effects. Limited data suggest that hepatotoxicity can occur in humans following acute oral exposure to sodium selenate, but no definitive studies were located regarding hepatic effects in humans after intermediate or chronic oral exposure to selenium compounds. Tests following an acute poisoning of a 15-year-old girl with sodium selenate revealed abnormally elevated serum bilirubin and alkaline phosphatase (Civil and McDonald 1978). Hepatic effects, such as changes in serum liver enzymes or liver morphology (identified by ultrasonography), have not been observed in humans at chronic dietary intakes of 0.0098 mg selenium/kg/day (Longnecker et al. 1991) or 0.025 mg selenium/kg/day (Yang et al. 1989a). Selenium-induced hepatotoxicity is documented in animals as summarized below. The lack of evidence of liver damage in humans due to selenosis, despite the animal data to the contrary, suggests a problem with the animal models of the disease.

Congestion and/or edema and hemorrhage in the liver have been reported in sheep following the acute oral (subroute not specified) administration of lethal levels of sodium selenate (Hopper et al. 1985) or sodium selenite (Smyth et al. 1990) and in mules and pigs following administration of lethal levels of sodium selenite (Miller and Williams 1940). A significant decrease in relative liver weight was reported for mice exposed to 9 ppm (0.82 mg selenium/kg/day) selenium as sodium selenite in drinking water for 14 days, but not to 3 ppm (0.38 mg selenium/kg/day) (Johnson et al. 2000). No effect on liver weight was observed for mice receiving up to 9 ppm (1.36 mg selenium/kg/day) selenium as selenomethionine in drinking water for 14 days (Johnson et al. 2000).

Administration of single gavage doses of selenium monosulfide to rats produced death and widespread hepatic necrosis in 3/6 animals dosed with 75 mg/kg, 1/2 animals dosed with 100 mg/kg, and 2/2 animals dosed with 125 mg/kg (Moore et al. 1996b).

Hepatic effects have also been reported following intermediate-duration exposure in pigs, but not in cattle. Pigs exposed for 7 weeks to either dietary organic selenium in dried plants (either *A. pruelongus* or *A. bisulcatus*) or sodium selenate (at 1.1 or 1.3 mg selenium/kg/day) exhibited diffuse swelling and vacuolar degeneration of hepatocytes (Baker et al. 1989). The doses used in this study reduced mean survival to only 44 days. Pigs exposed to sodium selenite in feed for 35 days at doses less than half as high as those tested by Baker et al. (1989) (0.47 versus 1.1 or 1.3 mg selenium/kg/day) exhibited no liver damage (Mahan and Magee 1991). A study of pigs treated with 0.08, 0.33, 0.59, or 1.07 mg

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selenium/kg/day as sodium selenite in the feed for 8 weeks found hepatic nodules/granules in two pigs treated with 0.59 or 1.07 mg selenium/kg/day (Mihailovic et al. (1992). The lesions were diagnosed as postdystrophic atrophic cirrhosis. However, only these two severely affected pigs (one from each of the highest dose groups of 40 animals each) were selected for histopathological examination. Hepatic effects were not observed in pigs fed selenium at 1.25 mg selenium/kg as organic selenium of the type(s) found in the plant *A. bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate for up to 6 weeks (Panter et al. 1996). Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in liver weight or histology (O'Toole and Raisbeck 1995).

Alterations or cirrhosis of the liver in experimental animals following intermediate or chronic oral exposure to selenium compounds have been reported by Bioulac-Sage et al. (1992), Fitzhugh et al. (1944), Halverson et al. (1970), Harr et al. (1967), Kolodziejczyk et al. (2000), Nelson et al. (1943), and Schroeder and Mitchener (1972). Halverson et al. (1966) reported reduced liver-to-body-weight ratios and increased bilirubin in rats administered 0.44 mg selenium/kg/day for 6 weeks as naturally occurring selenium in wheat. At this level, five of eight rats died. At a dose of 0.84 mg selenium/kg/day administered as sodium selenate in drinking water for 4–6 weeks, rats developed cirrhosis of the liver (Palmer and Olson 1974). At this level, two of six rats died.

Hepatic damage was observed in mice exposed to 0.2 mg selenium/kg/day as sodium selenite in food for 12 weeks (Skowerski et al. 1997a), and ultrastructural examination showed that the cytoplasm of the hepatocytes contained extremely large and irregularly-shaped vacuoles. Wistar rats administered 0.324 mg selenium/kg/day as sodium selenite in food for 12–14 weeks showed degenerative changes to the liver (not fully described in text) (Turan et al. 1999a). Livers of rats fed 0.002 or 0.005 mg selenium/kg/day as sodium selenite for 3 months showed damage that increased with dose (Kolodziejczyk et al. 2000). Rats from the 0.002 mg selenium/kg/day group had a distinct swelling of Küpffer cells in dilated sinusoidal vessels, mainly in the proximity of portal fields, and occasional necrotic areas comprising groups of hepatocytes, while livers from rats receiving 0.005 mg selenium/kg/day showed activation and swelling of the Küpffer cells in widened sinusoidal vessels, relatively abundant infiltrations of mononuclear cells into portal canals, and sporadic areas of necrosis within individual lobules.

Young rats treated with sodium selenite in the feed for 2 months had nodular hyperplasia at a dose of 0.2 mg selenium/kg/day. However, clinical tests of liver function (bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase activities) showed no

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significant changes (Bioulac-Sage et al. 1992). Diffuse panlobular vacuolar changes were reported in rats fed sodium selenite in the diet for 8 weeks at 0.45 mg/kg/day (Chen et al. 1993).

In a 2-year cancer study, acute toxic hepatitis was common among rats fed sodium selenite or sodium selenate at 0.25 mg selenium/kg/day or higher (Harr et al. 1967; Tinsley et al. 1967). Liver surfaces were mottled, and parenchymatous degeneration was present. Hepatic lesions occurred at a dose as low as 0.10 mg selenium/kg/day. Absolute liver weights decreased with increasing levels of sodium selenate or sodium selenite in the diet. The average liver weight of animals administered selenate (14.5 g) was twice the average liver weight of animals administered selenite (7.2 g); however, the average liver weight of control animals was not reported, and possible dose-related hepatic effects were not discussed by these authors.

Increased serum bile acids, suggesting cholestasis, were observed in rats treated with 1.57 mg selenium/kg/day as sodium selenate in drinking water for 13 weeks, but no effects were noted at 0.92 mg/kg/day (NTP 1994). In a 13-week drinking water study, hepatic effects were not observed in mice treated with sodium selenate at 7.17 mg selenium/kg/day, in mice treated with sodium selenite at doses up to 3.83 mg selenium/kg/day, or in rats treated with sodium selenite at doses up to 1.67 mg selenium/kg/day (NTP 1994). Increased serum aspartate aminotransferase and alanine aminotransferase activities were observed in mice treated by gavage with selenocystine at doses of 9.4 mg selenium/kg/day for 30 days (Sayato et al. 1993) or 4.7 mg selenium/kg/day for 90 days (Hasegawa et al. 1994). No effects on liver enzymes were observed in mice treated with selenocystine at 4.7 mg selenium/kg/day for 30 days (Sayato et al. 1993) or at 2.5 mg selenium/kg/day for 90 days (Hasegawa et al. 1994). Chronic dietary administration of selenium as seleniferous corn or wheat at doses ranging from 0.25 to 0.50 mg/kg/day for 24 months produced cirrhosis of the liver in rats (Nelson et al. 1943).

An increased incidence of amyloidosis of the major organs, including the liver, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p < 0.001$) of selenium-treated mice. Data for individual organs were not provided.

Selenium sulfide administered to rats daily by gavage for 13 weeks produced focal coagulation necrosis in the liver with infiltration by inflammatory cells. These changes developed at a dose of 31.6 mg selenium sulfide/kg/day, but not at a dose of 17.8 mg selenium sulfide/kg/day (NTP 1980c). In mice, on

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the other hand, oral intubation of selenium sulfide at 464 mg selenium sulfide/kg/day did not produce hepatic effects (NTP 1980c).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to selenium or selenium compounds.

In domestic and experimental animals, renal effects have been observed following both acute and chronic oral exposures to selenium compounds. Administration of a single oral (subroute not specified) dose of sodium selenite at 5 mg selenium/kg/day produced hydropic degeneration of the kidney in sheep (Smyth et al. 1990). In a study of the toxicity of L-selenomethionine to long-tailed macaques by nasogastric intubation, two animals administered 0.24 mg selenium/kg/day aspirated vomitus secondary to emesis, developed obvious gastritis, and died of anorexia, one after 10 days and the other after 15 days of administration (Cukierski et al. 1989). Histopathologic examination of the kidneys of these animals revealed glomerulonephritis and proximal convoluted tubule nephropathy. The study authors indicated that these changes were consistent with macaque fatal fasting syndrome and may not have resulted from the direct effects of L-selenomethionine. Following long-term ingestion of plants high in selenium, livestock suffering from alkali disease exhibited nephritis (Shamberger 1986). However, treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in kidney weight or histology (O'Toole and Raisbeck 1995).

A dose-related increase in degeneration of the renal papilla (described as mild to minimal) was observed in rats treated with selenate or selenite in the drinking water at about 0.5 mg selenium/kg/day for 13 weeks (NTP 1994). No evidence of renal toxicity was observed in rats given 0.3 mg selenium/kg/day in this study. In contrast to rats, the only kidney effect noted in mice treated with sodium selenate or selenite in the drinking water was increased relative kidney weight (NTP 1994). This effect, which occurred at 1.87 mg selenium/kg/day as selenate and 1.61 mg selenium/kg/day as selenite, was only noted at doses at which drinking water intake was decreased, leading the investigators to suggest that the effect may have been a result of dehydration. A similar increase in relative kidney weight associated with decreased water consumption was observed in mice consuming approximately 0.38 mg selenium/kg/day as selenite in drinking water, but no effect on kidney weight or water consumption was observed in mice consuming up to 1.36 mg selenium/kg/day as selenomethionine (Johnson et al. 2000). No renal effects were observed in pigs fed selenium at 1.25 mg selenium/kg as organic selenium found in the plant *A. bisulcatus* for up to 5 days, or D,L-selenomethionine or selenate for up to 6 weeks (Panter et al. 1996). No effects on the kidneys were observed in rats treated with selenite in the diet for 8 weeks at a dose of

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0.45 mg selenium/kg/day (Chen et al. 1993). Gavage treatment of mice with selenocystine for 30 days at a dose of 9.4 mg selenium/kg/day had no adverse effect on the kidneys (Sayato et al. 1993).

Rats chronically fed selenite in the diet were reported to exhibit more frequent and more severe nephritis than those given equivalent amounts of selenate (Harr et al. 1967); however, the study authors did not quantify these observations or statistically compare data from the two groups. An increased incidence of amyloidosis of the major organs, including the kidneys, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p < 0.001$) of selenium-treated mice. Data for individual organs were not provided.

A mixture of selenium sulfide and selenium disulfide administered to mice daily by gavage for 13 weeks at a dose of 464 mg selenium sulfides/kg/day produced an increase in the incidence and severity of interstitial nephritis compared with the controls, whereas a daily dose of 216 mg selenium sulfides/kg did not elicit renal toxicity (NTP 1980c). In rats, selenium sulfide by oral intubation at 31.6 mg selenium sulfides/kg/day for 13 weeks did not produce renal effects (NTP 1980c).

Endocrine Effects. A balance in selenium and iodine levels is needed for normal thyroid hormone metabolism. Selenium is an essential component of the iodothyronine 5'-deiodinase enzymes, which convert the prohormone thyroxine (T_4) to the active form, triiodothyronine (T_3) (Delange 2000; Köhrle 1994; St Germain and Galton 1997). Selenium is also a component of glutathione peroxidase (GPX), the main enzyme responsible for protecting thyroid cells against oxidative damage. Selenium deficiency causes decreases in metabolic clearance of iodothyronines, extrathyroidal production of T_3 , and thyroid iodine concentrations in experimental animals (Arthur and Beckett 1989, 1994; Behne and Kyriakopoulos 1993). Deficiency in both selenium and iodine has been associated with goiter and cretinism in humans and causes thyroid gland necrosis and fibrosis in rats (Delange 2000; Goyens et al. 1987; Vanderpas et al. 1990). Additional information on thyroid effects of selenium and iodine deficiency is discussed in Section 3.9. Thyroid hormone levels in humans and animals can also be affected by selenium supplementation; these effects include decreases in serum T_3 and T_4 levels and increases in serum TSH levels, suggesting suppression of thyroid hormone production, as discussed below.

A limited amount of information is available regarding endocrine effects in humans following oral exposure to selenium. Serum levels of thyroid and reproductive hormones were evaluated in a double blind 120-day study of healthy men (20–45 years old) who consumed a controlled diet of foods naturally

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high or low in selenium (Hawkes and Turek 2001). Eleven subjects were fed 0.0006 mg/kg/day of selenium in the diet for the first 21 days of the study, followed by 0.0002 µg selenium/kg/day (6 subjects) or 0.004 mg selenium/kg/day (5 subjects) for 99 days. Blood samples were analyzed for serum levels of selenium, thyroid hormones (T₃ and TSH), and reproductive hormones (testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone) during week 3 (baseline), week 17 (ending value), and at several interim time points.

Selenium levels in blood plasma began to change within 3 days of starting the low- and high-selenium diets and progressively continued throughout the study (Hawkes and Turek 2001). By week 17, mean plasma selenium concentrations had increased by 109% in the high-selenium group and decreased by 38.5% in the low-selenium group. Group mean serum T₃ concentrations (averages of within-subject changes from baseline) were significantly different in the low-selenium subjects and high-selenium subjects at all time points, but the changes are insufficient to be considered adverse as discussed below. In the low-selenium group, serum T₃ levels increased an average of 14 and 8% from baseline at weeks 8 and 17, respectively. In the high-selenium group, serum T₃ levels decreased an average of 23 and 11% from baseline at weeks 8 and 17, respectively. Analysis of variance (ANOVA) showed a significant main effect of dietary selenium on serum T₃ concentrations, as well as a significant selenium x time interaction, indicating that the changes in T₃ levels decreased over time. Although the decreases in serum T₃ in the high-selenium group and increases in serum T₃ in the low-selenium group lessened in magnitude during the study, all group mean values appear to have remained within the normal range. The baseline and week 17 serum total T₃ values (mean±SD) were 1.82±0.36 and 1.57±0.07 nmol/L in the high-selenium group, and 1.57±0.25 and 1.64±0.16 nmol/L in the low-selenium group, compared to the normal human range of 1.1–2.7 nM/L (Stockigt 2000), indicating that the changes in serum T₃ were subclinical and not toxicologically significant. Serum TSH concentrations increased significantly by 32% over its baseline concentration in the high-selenium group, but did not change significantly in the low-selenium group. Baseline and ending mean TSH values in the high-selenium group were 2.25±0.81 and 2.96±1.05 mU/L, respectively, both of which are in the normal range of 0.3–4.0 mU/L (Stockigt 2000). The lack of clinically significant changes in serum T₃ and TSH values is not surprising because the study was designed as a nutritional study and not as a toxicological study; the selenium intakes bracketed the current recommended dietary allowance (RDA) (~0.8 µg Se/kg/day) and were well below the tolerable upper limit level (~5.7 µg Se/kg/day) recommended by the Food and Nutrition Board (NAS 2000). There were no significant changes in serum levels of free or total testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, or progesterone. This study also found no adverse immunologic or male reproductive changes as summarized in Sections 3.2.2.3 and 3.2.2.5.

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An examination of thyroid hormone levels in lactating women residing in areas of Venezuela with high levels of selenium in the soil (selenium intake ranged from 250 to 980 µg per day as estimated from selenium content of breast milk) revealed a significant decrease in serum T₃ levels, as compared with women having normal selenium intakes (90–350 µg/day), but these hormone levels remained within the normal range (Brätter and Negretti De Brätter 1996). Additionally, a significant inverse correlation for selenium and serum T₃ concentration was found using the Spearman Rank test. The study authors noted that the effect of selenium on T₃ levels became significant at dietary intake levels of 350–450 µg/day. No significant alterations in serum T₄ or TSH levels or correlations with selenium intake were found.

Twenty weeks of selenium supplementation (10, 20, 30, or 40 µg/day) of New Zealanders who normally consume a diet low in selenium (unsupplemented intake of 28–29 µg/day), but show no signs of deficiency, produced a reduction in T₄ concentration in all groups (Duffield et al. 1999). However, only the differences between the 10 µg-group and controls and the combined supplemented individuals and controls were significant. T₃ and TSH levels were not measured. Thyroglobulin concentration did not change significantly with supplementation.

In a study of 68 male Latvian fish consumers (Hagmar et al. 1998), a significant inverse correlation was found between serum levels of selenium and TSH. No correlation was found between serum selenium concentration and the serum concentrations of T₃ or T₄. No measurements were made of dietary selenium intake.

Selenium supplementation has been shown to affect type-I-deiodinase activity in male rats (Behne et al. 1992; Eder et al. 1995; Hotz et al. 1997). Exposure to 0.055 or 0.27 mg selenium/kg/day as sodium selenite in food for 40 days produced a significant decrease (approximately 50%) in serum levels of T₃ and a nonsignificant reduction in type-I-deiodinase activity compared with rats receiving 0.009 or 0.026 mg selenium/kg/day (Eder et al. 1995). Exposure to 0.27 mg selenium/kg/day did not produce any other adverse signs, such as weight loss or decreased food consumption, and serum T₄ levels were similar in all groups.

Exposure of weanling male Sprague-Dawley rats to 0.09 mg selenium/kg/day as sodium selenate in food for 6 weeks produced a significant (~30%) increase in TSH, compared with controls receiving 0.009 mg selenium/kg/day (Hotz et al. 1997). Serum T₃ and T₄ levels and thyroid glutathione peroxidase levels were unaffected by dietary selenium. Kidney type-I-deiodinase levels were decreased (~10%) in high

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selenium animals compared with controls, but the differences were not significant, and liver type-I-deiodinase levels were unaffected by dietary selenium. Iodine-deficient diets produced greater thyroid glutathione peroxidase activity at each dietary level of selenium, and the greatest activity was in rats with high selenium.

No significant changes in thyroid levels of T₃ or T₄ were found in male Wistar rats fed diets containing high selenium (0.105 mg selenium/kg/day as sodium selenite or 0.118 mg selenium/kg/day as L-selenomethionine) for 3 months, compared with controls receiving adequate selenium (0.0015 mg selenium/kg/day as sodium selenite) (Behne et al. 1992). However, rats eating the high selenium diet showed a significant reduction in hepatic type I deiodinase activity, compared with controls, with a 29% reduction in the production rate of T₃ from T₄ and a 45% reduction in the production rate of 3,3'-diiodothyronine from T₄.

Many studies have documented reduced body weight gain in young animals treated with selenium compounds, and abnormal weight loss in older animals (Grønbaek et al. 1995; Halverson et al. 1966; Harr et al. 1967; Jacobs and Forst 1981a; Johnson et al. 2000; Nelson et al. 1943; NTP 1994; Palmer and Olson 1974; Panter et al. 1996; Schroeder 1967; Tarantal et al. 1991; Tsunoda et al. 2000). There is evidence to suggest that these effects may be due in part to the interactions of selenium or selenium compounds with hormones that regulate normal growth and body weight. In a 14-day study suggesting that selenium may inhibit pituitary function, Thorlacius-Ussing (1990) treated nursing rats with sodium selenite in drinking water (0.64 or 0.96 mg/kg/day). The resulting decrease in the body weight gain of the pups observed at both doses may be associated with a reduction in somatomedin C levels (no other hormone levels were tested), and the weight deficiency could be reversed by administration of a growth hormone.

Postweanling female Wistar rats treated with sodium selenite (0.64 mg selenium/kg/day) in drinking water for 3 or 6 weeks exhibited decreased weight gain and decreased somatomedin C serum concentrations. When the selenium supplement was removed after 3 weeks, body weight gain returned to normal, but the serum somatomedin C concentrations did not return to control levels. Growth hormone secretion in response to growth hormone releasing factor was also reduced in the selenium-exposed group (Thorlacius-Ussing et al. 1988). Serum somatomedin C levels were not significantly different among three exposure categories (<200, 201–240, and >240 ng selenium/mL) in 44 long-term residents of seleniferous areas in South Dakota, despite >50% differences in serum, whole blood, and toenail selenium levels among the groups (Salbe et al. 1993). A 10% reduction in body weight and a reduction in tibia lengths, compared to pair-fed controls, were found in rats provided with sodium selenite in the drinking water at 0.46 mg selenium/kg/day for 35 days (Grønbaek et al. 1995). A significant reduction in insulin-

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like growth factor-binding protein-3 was also noted. The investigators concluded that the reduction in growth caused by excess selenium is not due to reduced caloric intake.

Selenium administered in drinking water for 13 weeks at doses up to 1.57 and 7.17 mg selenium/kg/day as selenate in rats and mice, respectively, and 1.67 and 3.83 mg selenium/kg as selenite in rats and mice, respectively, failed to cause changes in the weights or histology of the thyroid, adrenal glands, parathyroid, or pancreas (NTP 1994).

Lambs given a single oral (subroute not specified) dose of 5 mg selenium/kg as sodium selenite exhibited cytoplasmic flocculation of the pancreas (Smyth et al. 1990). Increased pancreas weights were observed in rats fed organic selenium (seleniferous wheat) at a dose of 0.4 mg selenium/kg/day for 6 weeks (Halverson et al. 1966). Chronic exposure of rats fed sodium selenite or sodium selenate in their diet for a lifetime was associated with pancreatic damage. Although Harr et al. (1967) reported a dose-related increase in the incidence and severity of pancreatic lesions in treated rats, they did not specify the lowest dose at which pancreatic lesions were observed.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in weight or histology of the pancreas, adrenal glands, thyroid, or pituitary gland (O'Toole and Raisbeck 1995).

An increased incidence of amyloidosis of the major organs, including the adrenal gland, was observed in mice following lifetime exposure to sodium selenate or sodium selenite in drinking water at a level of 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). This effect was noted in 30% of control mice and 58% ($p < 0.001$) of selenium-treated mice. Data for individual organs were not provided.

Dermal Effects. Jensen et al. (1984) described both marked alopecia and the deformity and loss of fingernails in a woman who had consumed a selenium supplement containing 31 mg total selenium (in the form of sodium selenite and elemental selenium) per tablet for 77 days. The woman consumed one tablet each day in addition to vitamin supplements (vitamins C, A, D, E, B complex) and a mineral supplement "labeled as containing all 72 trace elements in undefined quantities." In epidemiological studies of populations chronically exposed to high levels of selenium in food and water, investigators have reported discoloration of skin, pathological deformity and loss of nails, loss of hair, and excessive tooth decay and discoloration (Smith et al. 1936; Yang et al. 1983, 1989a, 1989b). The 1989 studies by Yang et al. follow up their original 1983 study of Chinese populations living in areas classified as having

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low-, medium-, and high-selenium exposure based on local soils and food supplies. The average and standard error of selenium intakes in the low-, medium-, and high-intake regions were 0.0012 ± 0.00009 , 0.0037 ± 0.0004 , and 0.025 ± 0.001 mg/kg/day, respectively. The whole blood (average \pm standard error) concentrations of selenium in the low-, medium-, and high-intake regions were 0.16 ± 0.00 , 0.35 ± 0.02 , and 1.51 ± 0.05 mg/L, respectively. The estimated daily dietary selenium intake required to produce these symptoms in an area of China characterized by endemic selenosis was at least 0.016 mg selenium/kg/day (Yang et al. 1989a). This corresponds to a blood concentration of 1.054 mg/L and an estimated daily intake of 0.91 mg/day, assuming a 55-kg Chinese man or woman and using the regression analysis provided by Yang et al. (1989b). The NOAEL from the highest intake population not affected by nail disease is 0.015 mg selenium/kg/day, which corresponds to a blood concentration of 0.97 mg/L. Foods that contributed the greatest levels of selenium were smoked pork, coal-dried corn, chestnuts, pumpkin seeds, dried fruits, and garlic. It has been noted that the selenosis problem in China began when coal with high levels of selenium was burned as the main source of fuel (Whanger 1989). Food was cooked and dried over the open flame, adding selenium to the food. In addition, the people breathed large amounts of smoke, but the contribution of volatilized selenium to the total dose of selenium has not been adequately characterized (Whanger 1989). Coal was also burned on the fields as a fertilizer source. Environmental selenium concentrations in the low-, medium-, and high-intake regions were 0.37–0.48, 0.73–5.66, and 7.06–12.08 mg/kg in soil, and 370, 1,720, and 12,270 μ g/L in water, respectively (Yang et al. 1989b).

No evidence of nail disease was observed in a population living on selenium-rich ranches in the western United States (Longnecker et al. 1991). Doses of selenium were calculated to be between 0.001 and 0.01 mg/kg/day, corresponding to a maximum intake of 0.724 mg/day. Whole blood selenium concentrations were 0.18–0.67 mg/kg. Although these values for the United States are consistent with studies of the Chinese population, only one or a few individuals ingested the highest doses.

The highest selenium intake for villagers in a high-selenium area of China in which endemic selenosis did not occur was estimated at 1.51 mg selenium/person/day (0.027 mg selenium/kg/day), with the average dietary selenium intake in this area of selenosis occurrence estimated to be 3.2 mg selenium/person/day (0.058 mg selenium/kg/day) (Yang et al. 1983). The lowest daily dietary selenium intake associated with dermal effects, 0.91 mg selenium/day, was converted to equivalent daily doses from food (0.016 mg/kg/day) for presentation in Table 3-2.

Five individuals from the high selenium region of China described by Yang et al. (1989a) who had been diagnosed with overt signs of selenosis (hair loss and nail sloughing) in 1986 were reexamined in 1992

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(Yang and Zhou 1994). The results of this examination showed that these individuals had recovered from selenosis (overt symptoms of nail sloughing were absent) and that the average selenium concentrations in their blood had fallen from 1,346 to 968 µg/L. The corresponding dietary intakes of selenium were 1,270 and 819 µg/day. This study has been used to establish a LOAEL of 0.023 mg selenium/kg/day and a NOAEL of 0.015 mg selenium/kg/day. Based on the occurrence of these dermal effects, a chronic oral MRL of 0.005 mg selenium/kg/day has been derived from the NOAEL, as described in the footnote in Table 3-2 and detailed in Appendix A. This MRL is approximately 6 times greater than the NAS (2000) RDA for selenium of 55 µg/day (~0.0008 mg/kg/day).

In a 30-day study of oral administration of L-selenomethionine to long-tailed macaques, skin lesions appeared on the forearm of one of two macaques given 0.01 mg selenium/kg/day. However, the limited number of animals precludes identifying the dose as a LOAEL for dermal effects (Cukierski et al. 1989). Pigs receiving dietary administration of the same doses of selenium for 35 days exhibited hoof cracking (Mahan and Magee 1991). Symmetrical hair loss, dry scaling skin, and cracked overgrown hooves were observed in one of five pigs and three of five pigs fed sodium selenate or D,L-selenomethionine at a dose of 1.25 mg selenium/kg/day for up to 6 weeks, respectively (Panter et al. 1996). In an experiment limited to a duration of 5 days because of severe paralysis, similar dermal effects were not observed in pigs fed 1.25 mg selenium/kg/day as selenium contained in the plant *A. bisulcatus*. The form of selenium in *A. bisulcatus* is unknown, although Panter et al. (1996) indicate that it is nonprotein.

Exposure of pigs to feed containing 54 mg/kg selenium for 1–7 days resulted in severe toxicity and death of several animals; however, none of the pigs developed coronitis or hoof separation (Penrith and Robinson 1996). Skin from four pigs with alopecia was examined about a month after exposure and was found to have epidermal thickening due to acanthosis and hyperkeratosis, vacuolar degeneration of the basal cells and acanthocytes, necrosis of individual keratinocytes, and serocellular crusts.

In the late 19th and the early 20th century, livestock grazing on plants growing on seleniferous soils in areas of the Great Plains of the United States suffered from alkali disease attributed to the high selenium content of some plants. Alkali disease in horses, cattle, and swine is characterized by alopecia, inflammation at the coronary band, followed by cracked or malformed hooves and rough hair coat (Draize and Beath 1935). Daily selenium intakes associated with these effects were not quantified. However, treatment of steers with selenomethionine in food at doses of 0.288 mg selenium/kg body weight/day or selenite at doses of 0.808 mg selenium/kg/day for 120 days produced hoof lesions (O'Toole and Raisbeck 1995). In intermediate-duration studies, cracked hoof walls have been observed in pigs fed selenate,

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selenite, or an unspecified form of selenium at doses of 0.25 mg selenium/kg/day and greater (Baker et al. 1989; Mahan and Magee 1991; Mihailovic et al. 1992; Wahlstrom and Olson 1959b). Poor quality of the hair coat has also been reported in mice administered sodium selenite or selenate in the diet at 0.57 mg selenium/kg/day (Schroeder and Mitchener 1972). Exposure of female BALB/c mice to 0.21 mg selenium/kg/day for 6 months from diets containing selenium as sodium selenite resulted in alopecia around the nose (Boylan et al. 1990).

No studies were located regarding dermal effects in humans or other animals after oral exposure to selenium sulfide or selenium disulfide.

Ocular Effects. A case-control study using a hospital discharge register indicated that there was no correlation between low serum selenium concentrations and cataract occurrence in humans (Knekt et al. 1992). Since this is a case-control study, it does not provide information on the potential dietary factors, exposure to specific selenium compounds, or duration of exposure.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days did not produce any changes in the histology of the eyes (O'Toole and Raisbeck 1995). Selenium given to rats and mice in drinking water for 13 weeks at up to 1.6 and 7.2 mg selenium/kg as selenate, respectively, or 1.7 and 3.8 mg selenium/kg as selenite, respectively, did not cause any ocular effects (NTP 1994).

Body Weight Effects. Two studies reported body weight effects in humans after oral exposure to selenium. Selenium intake was found to affect body weight in a study of 11 men (20–45 years old) who were fed 0.0006 mg/kg/day of selenium in the diet for the first 21 days of the study, followed by diets naturally low (0.0002 µg selenium/kg/day, 6 subjects) or high (0.004 mg selenium/kg/day, 5 subjects) for 99 days at 2,800 kcal/day (Hawkes and Keim 1995). Despite minor adjustments of intake to maintain body weight, by the 6th week, the high selenium group started to gain weight relative to the low selenium group, and the difference between the two groups became significant after the 10th week. A similar increase in lean body mass was observed in both groups. The study was designed as a nutritional study and not as a toxicological study, as the selenium intake levels were well below the tolerable upper limit level (~5.7 µg Se/kg/day) recommended by the Food and Nutrition Board (NAS 2000). The weight gain observed in this study therefore has nothing to do with weight loss due to selenosis.

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A study that compared children from seleniferous and nonseleniferous areas of Venezuela found slightly reduced height and weight (no statistical analysis was performed) for the children from the seleniferous area (Jaffe et al. 1972). However, the children from the seleniferous zone had a poorer diet, consumed less milk and meat, and had a greater incidence of intestinal parasites, which may account for the differences observed.

In contrast, reduced growth rates of young animals and reduced body weight in older animals are common observations associated with oral administration of excess sodium selenate, sodium selenite, or organic selenium compounds to experimental animals (Boylan et al. 1990; Cukierski et al. 1989; Donaldson and McGowan 1989; Grønbaek et al. 1995; Halverson et al. 1966; Harr et al. 1967; Hasegawa et al. 1994; Johnson et al. 2000; Nelson et al. 1943; NTP 1994, 1996; Palmer and Olson 1974; Panter et al. 1996; Penrith and Robinson 1996; Raisbeck et al. 1996; Sayato et al. 1993; Schroeder 1967; Tarantal et al. 1991; Thorlacius-Ussing 1990; Tsunoda et al. 2000; Turan et al. 1999a). This reduction in growth is often accompanied by reduced food and water consumption, and in dietary or drinking water studies, may be an effect of poor palatability of selenium compounds. However, reduced growth has also been observed in gavage studies (Cukierski et al. 1989; Hasegawa et al. 1994; Sayato et al. 1993) and, as discussed under endocrine and neurological effects, the growth retardation may have an endocrine or neurotransmitter component. Selenium effects on the levels of thyroid hormones (Behne and Kyriakopoulos 1993; Behne et al. 1992; Eder et al. 1995; Hotz et al. 1997), dopamine metabolites (Tsunoda et al. 2000), insulin-like growth factor-binding protein-3 (Grønbaek et al. 1995), and somatomedin C (Thorlacius-Ussing 1990) have been observed in selenium-treated animals, although somatomedin C was not a sensitive end point in humans from a high selenium area of South Dakota (Salbe et al. 1993).

Other Systemic Effects. Urinary excretion of selenium was about twice as great in children with a high incidence of dental caries than in children with a low incidence of caries (Hadjimarkos 1969b). Possible confounding factors (e.g., fluoride status and socioeconomic status) were not considered, however. In Yang et al. (1989a), the incidence of mottled teeth in the medium- and high-selenium groups was increased, but the effect was attributed to interactions between selenium and fluoride.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding adverse immunologic or lymphoreticular effects in humans after oral exposure to selenium or selenium compounds. Immune system effects were evaluated in a 120-day double blind study of healthy men who ingested a controlled diet of foods naturally low or high in selenium (Hawkes et al. 2001). Eleven subjects were fed 0.0006 mg selenium/kg/day in the diet for 21 days (baseline period), followed by 0.0002 mg/kg/day (6 subjects) or 0.004 mg/kg/day (5 subjects) for the following 99 days. The results show that the high-selenium diet was not immunotoxic and had some mild and transient immune-enhancing properties. There is an indication that selenium supplementation increased the secondary immune response to diphtheria vaccine when rechallenged at the end of the study. The mean within-subject ratio of diphtheria antibody titers 14 days after reinoculation (day 116) to titers 14 days after the initial challenge at baseline (day 19) was significantly greater in the high-selenium group than in the low-selenium group (2.7 ± 1.8 -fold vs. 0.9 ± 0.6 -fold, $p=0.03$). Lymphocyte counts were significantly increased in the high-selenium group on day 45, but not at the end of the study, and there were no clear effects of selenium on numbers of activated or cytotoxic T-cells. The proliferative response of peripheral lymphocytes to stimulation with pokeweed mitogen (a B-cell mitogen) was significantly higher in the high-selenium group than in the low-selenium group on days 45 and 72, although not at the end of the study. There was no selenium-induced lymphocyte proliferation in response to T-cell mitogens (phytohemagglutinin or concanavalin A), or changes in lymphocyte phenotypes, serum immunoglobulins (IgA, IgG, IgM), complement fractions, natural-killer cell activity, delayed-type hypersensitivity skin responses to seven recall antigens (tuberculin purified-protein derivative, mumps, tetanus toxoid, candida, trichophyton, streptokinase streptase, and coccidioidin), or antibody responses to diphtheria-tetanus and influenza vaccines. This study was designed as a nutritional study and not as a toxicological study, as the selenium intake levels were well below the tolerable upper limit level ($\sim 5.7 \mu\text{g Se/kg/day}$) recommended by the Food and Nutrition Board (NAS 2000).

Other human studies also indicate that selenium contributes to enhancing immune function (Baum et al. 1997; Kiremidjian-Schumacher et al. 1994; Peretz et al. 1991). Lymphocyte response was enhanced by dietary selenium, as measured by the T-lymphocyte proliferative response to pokeweed mitogen in elderly people taking a selenium-enriched yeast supplement (0.0014 mg/kg/day for 6 months) (Peretz et al. 1991). This finding is similar to results of the Hawkes et al. (2001) study summarized above, although it was noted that the elderly as a group generally tend to have both lower blood selenium concentrations and lower lymphocyte proliferation than the general population. Dietary supplementation with approximately $0.001 \text{ mg selenium/kg/day}$ (as sodium selenate) for 8 weeks caused increased proliferation of active T

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cells in a group of 11 volunteer subjects (Kiremidjian-Schumacher et al. 1994). The lymphocytes in the exposed subjects had an increased response to stimulation with alloantigen and developed into cytotoxic lymphocytes capable of destroying tumor cells. There was a 118% increase in cytotoxic lymphocyte-mediated tumor cytotoxicity, as well as an 82.3% increase in natural killer cell activity, compared to baseline values. The selenium supplementation regimen used in this study did not cause significant increases in selenium levels in the plasma or red blood cells.

Immune function was evaluated in 40 volunteers from a Finnish population with low blood selenium concentrations that were supplemented with selenium or placebo for 11 weeks (Arvilommi et al. 1983). At the end of the supplementation period, plasma selenium levels were 74 µg/L in the placebo group and 169 µg/L in the supplemental group. Intracellular killing of *Staphylococcus aureus* by granulocytes was slightly lower in the placebo group than in the selenium group (77.2% compared to 85.2%, $p < 0.05$). No significant changes were observed in phagocytosis, chemotactic factor generation, antibody or leukocyte migration inhibitory factor production by lymphocytes, or proliferative responses to the T-cell mitogens phytohemagglutinin or concanavalin A.

There is evidence that selenium has a role in protecting patients with HIV virus. Immune parameters and nutrients known to affect immune function were evaluated at 6-month intervals in 125 HIV-1-seropositive drug-using men and women (Baum et al. 1997). When all factors that could affect survival were considered jointly, only reduced number of CD4 helper T cells over time and selenium deficiency were significantly associated with mortality. Low plasma selenium (< 85 µg/L) represented a significantly greater risk factor for mortality than low helper T cell counts, and conferred a more significant risk than any other nutrient studied, indicating that selenium-deficient HIV patients were more likely to die from HIV infection than those with adequate levels of selenium.

Studies of mice, rats, and cattle suggest that exposure to high doses of sodium selenite, but not selenomethionine, may reduce immunological responses (Johnson et al. 2000; Koller et al. 1986; Raisbeck et al. 1998; Yaeger et al. 1998). BALB/c mice (five males/group) were exposed to drinking water containing 0, 1, 3, and 9 ppm selenium as sodium selenite (0.024, 0.17, 0.38, and 0.82 mg selenium/kg/day) or seleno-L-methionine (0.024, 0.17, 0.47, and 1.36 mg selenium/kg/day) for 14 days (Johnson et al. 2000). The mice exposed to sodium selenite showed significant decreases in the relative spleen weight at 9 ppm and the relative thymus weight at 3 and 9 ppm. The number of splenocytes in the spleens of the 9 ppm group was reduced by 62%. Single-cell splenocyte cultures were made from the spleens of treated animals and used to determine the effects of selenium treatment on mitogen-induced

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lymphocyte blastogenesis and cytokine production. Cultured splenic lymphocytes from mice exposed to 9 ppm selenium as sodium selenite showed a significant (260%) increase in the basal rate of proliferation and a nonsignificant increase in mitogen-induced proliferation. Exposure to 9 ppm selenium as sodium selenite also produced a significant increase in the amount of tumor necrosis factor α (TNF α) and interleukin-1 β (IL-1 β) produced by lipopolysaccharide (LPS)-stimulated splenic macrophages. However, the results of this experiment must be interpreted with caution as treatment with 9 ppm selenium as sodium selenite also produced a large and statistically significant decrease in food (21%) and water (43%) consumption, so that some of the effects observed (e.g., changes in organ weights) may reflect effects of dehydration rather than selenium toxicity. In contrast, the similar groups of mice treated with up to 9 ppm selenium as seleno-L-methionine (up to 1.36 mg selenium/kg/day) showed no significant changes in body weight gain, organ weights, water consumption, or food consumption compared with controls. There were no changes in the basal or mitogen-stimulated lymphocyte proliferation following treatment with seleno-L-methionine, and no alteration in the production of TNF α or IL-1 β from splenic macrophages was observed.

Another study in BALB/c mice examined the effects of consumption for 47 days of drinking water containing 7 ppm selenium as selenocystine, selenomethionine, or sodium selenite on immune function (Raisbeck et al. 1998). On the 14th day of the experiment, the mice received a subcutaneous injection of ovalbumin (OVA). Examination of mitogen-stimulated blastogenesis, B-cell function, and IgG concentrations at the end of the experimental period showed a significant decrease in B-cell function for mice treated with the two organic forms of selenium and a significant reduction in the concentration of OVA-specific antibodies for animals treated with any of the three forms of selenium. Total IgG concentration and OVA-stimulated blastogenesis did not vary between groups.

Rats given sodium selenite in drinking water at 0.7 mg selenium/kg/day for 10 weeks exhibited reduced humoral antibody (IgG) production in response to an administered antigen, and reduced prostaglandin synthesis, but there was no effect on natural killer cell (NKC) cytotoxicity (Koller et al. 1986). At lower doses (0.07 or 0.28 mg selenium/kg/day), NKC cytotoxicity was significantly increased, enhancing the immune response to antigenic stimulation, although the delayed-type hypersensitivity (DTH) and prostaglandin E₂ synthesis were significantly reduced. Selenium administration did not affect the ability of resident peritoneal cells to produce interleukin IL-1. Given the enhanced NKC activity at 0.07 and 0.28 mg selenium/kg/day, but not at 0.7 mg selenium/kg/day, and given the reduced antibody and prostaglandin synthesis at 0.7 mg selenium/kg/day, the dose of 0.7 mg selenium/kg/day is identified as

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the lowest LOAEL. A NOAEL cannot be identified because of the conflict between enhanced NKC activity and reduced DTH and prostaglandin E₂ synthesis occurring at the same dose levels in this study. Antibody responses to ovalbumin were significantly lower in five male antelope (*Antilocapra americana*) fed a diet containing 15 ppm selenium (a mixture of alfalfa and hay naturally high in selenium) for 164 days than in controls fed a similar diet containing only 0.3 ppm selenium, but there was no difference in total globulin concentration between groups (Raisbeck et al. 1996). No clinical signs of selenosis or treatment-associated lesions were observed in these animals.

Treatment of steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days produced symptoms of selenosis (hoof lesions), but did not produce any changes in the weight or histology of the spleen or thymus or in the histology of the lymph nodes (O'Toole and Raisbeck 1995).

Leukocyte function was significantly reduced in pregnant cows supplemented with 0.135 mg/kg/day selenium for 3 months from diets that contained 0.25 (control), 6, or 12 ppm selenium as sodium selenite. Treated animals showed a significant decrease in forced antibody production and a depression in mitogenic response compared with controls (0.005 mg selenium/kg/day) (Yaeger et al. 1998). No clinical signs of selenium toxicosis were observed in any of the cows during the experiment.

As selenium can enhance some immune system functions, selenium may have a normal physiological function in the immune system. This is supported by an 8-week study in which treatment of mice with selenium as sodium selenite (0.33 mg selenium/kg/day, dietary) resulted in enhanced ability of cytotoxic T-lymphocytes to destroy tumor cells (Kiremidjian-Schumacher et al. 1992).

Selenium appeared to play a protective role against viral infection in rats (Beck et al. 1995). When selenium-deficient rats were inoculated with a benign strain of Coxsackie's virus (CVB3/0), six separate point mutations were identified with the progression of virulence, causing myocarditis. Coxsackie's virus appears to act as a cofactor in the development of the myocarditis; this was shown when the virus was isolated from blood and tissue of people with Keshan disease (a cardiomyopathy particularly prevalent in selenium-deficient growing children and women of child-bearing age).

No studies were located concerning immunological or lymphoreticular effects in humans or experimental animals following oral exposure to selenium sulfide or selenium disulfide.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects following oral exposure to selenium or selenium compounds for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Following acute oral exposure to selenium compounds in humans, aches and pains and irritability (Civil and McDonald 1978), as well as chills and tremors (Sioris et al. 1980) have been reported. The dizziness associated with selenium inhalation exposure has not been documented after selenium ingestion.

In a 1964 study, Rosenfeld and Beath reported listlessness, a general lack of mental alertness, and other symptoms of selenosis in a family exposed for approximately 3 months to well water containing 9 mg selenium/L (0.26 mg selenium/kg/day from drinking water). All of the symptoms resolved after use of the seleniferous water was discontinued. Because Rosenfeld and Beath (1964) did not estimate the family's exposure to dietary selenium, it is not possible to identify the total daily selenium dose associated with the symptoms of selenosis in this family.

In a dietary study of 11 men in a metabolic unit, selenium intake (80 µg/day for the first 21 days, then either 13 [n=6] or 356 [n=5] µg/day for 14 weeks) was reported to have no significant effect on mood, as measured using the Bi-Polar form of the profile of mood states (POMS) (Hawkes and Hornbostel 1996). However, subjects with initially low selenium levels did show significantly greater decreases in mood scores during selenium depletion.

In areas of the People's Republic of China where populations suffer from chronic selenosis, peripheral anesthesia and pain in the limbs were reported (Yang et al. 1983). In extreme cases, exaggerated tendon reflexes, convulsions, and some paralysis and hemiplegia occurred (Yang et al. 1983). These latter cases were associated with an estimated daily dietary intake of selenium of at least 3.22 mg selenium/person/day, averaging 4.99 mg selenium/person/day (Yang et al. 1983). Assuming a weight of 55 kg for Chinese men (Yang 1989b), these dietary levels represent 0.027 mg selenium/kg/day and 0.09 mg selenium/kg/day, respectively. In another high selenium area, no neurological effects were observed in individuals who consumed up to 1.51 mg selenium/day (0.027 mg/kg/day) (Yang et al. 1983). Danish geriatric patients with a mean age of 75.3 years were given daily either a placebo or an antioxidant cocktail containing 0.004 mg/kg/day of selenium as L-selenomethionine along with zinc, vitamins C, A,

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B6, and E, and gamma-linolenic acid. After 1 year, whole blood selenium concentrations increased in the treated group, and slight but significant improvements in psychological scores were observed (Clausen et al. 1989). Because a mixture of nutrients was administered, the improvement in the patients cannot be attributed to selenium. People living on ranches with high selenium soils where selenium toxicity in livestock had historically been observed were compared to randomly selected residents in Wyoming and South Dakota. Daily selenium intake was measured by analysis of duplicate food portions. Subjects received a complete physical exam with a symptom questionnaire and laboratory tests. There were no biologically significant changes in clinical signs or blood chemistry. Calculated doses ranged from 0.001 to 0.01 mg selenium/kg/day in the diet (Longnecker et al. 1991).

An increased incidence (4 observed cases, 0.97 expected, standardized incidence ratio=4.14, 95% confidence interval [CI]=1.13–10.60) of amyotrophic lateral sclerosis, a human motor neuron disease of unknown origin, was reported for a cohort of 5,182 residents of Reggio Emilia, Italy who had been exposed to drinking water containing increased selenium (7–9 µg/L) from 1972 to 1988, compared with the incidence among residents of the surrounding area who had received municipal water containing <1 µg/L selenium (Vinceti et al. 1996). A subcohort of 2,065 of these individuals who had been exposed from 1974 (the earliest date for which a chemical analysis of the municipal tap water was available) was also examined and found to have an increased incidence ratio (4 observed cases, 0.47 expected, standardized incidence ratio=8.59, 95% CI=2.34–21.98). However, the study is limited by a water level of selenium that is not generally considered to be high, a lack of individual measurements of selenium exposure, and insufficient information on confounding variables. The lack of data on selenium status indicates that the study found a correlation but not causation.

In a 30-day study of the administration of L-selenomethionine to long-tailed macaques, severe hypothermia was observed in two of five animals administered 0.12 mg selenium/kg/day, but not in any of the eight animals receiving 0.08 mg selenium/kg/day (Cukierski et al. 1989). However, the increased incidence of hypothermia was not statistically significant. Following 1 week of treatment, all animals administered L-selenomethionine, including the two macaques treated with 0.01 mg selenium/kg/day, exhibited increased drowsiness and lethargy (Cukierski et al. 1989).

Symmetrical focal poliomyelomalacia and other forms of paralysis were seen in swine exposed to 0.58–2.1 mg selenium/kg/day after both acute and intermediate exposures (Baker et al. 1989; Goehring et al. 1984; Harrison et al. 1983; Mihailovic et al. 1992; Panter et al. 1996; Penrith and Robinson 1996; Stowe et al. 1992; Wilson et al. 1983, 1988, 1989). This lesion was noted in animals that showed ataxia,

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inability to stand, and paralysis of the hind limbs. Additionally, bilateral lesions were noted in the ventral horns of the cervical and lumbar/sacral intumescences of the spinal cord. Necrosis and cavitation were evident in the larger lesions (Harrison et al. 1983). Bilateral lesions were also observed in several nuclei of the brain stem and in the reticular formation (Wilson et al. 1983). Wilson et al. (1983) reproduced the syndrome in growing pigs by feeding them sodium selenite at 50 mg selenium/kg in the diet for 20–40 days. The study authors did not provide sufficient information to calculate doses on a mg selenium/kg body weight basis, but assuming that young swine consume approximately 4% of their body weight each day, this dose was approximately 2.1 mg/kg/day.

In a study of weaned 5-week-old pigs, a dose of 1.3 mg selenium/kg/day given as sodium selenite in capsules killed all eight pigs within 10 days. Histopathological lesions were found in the brain and spinal cord (Wilson et al. 1989). In a study in which pigs were fed 1.25 mg selenium/kg/day in the form of *A. bisulcatus*, D,L-selenomethionine, or selenate, the selenium in *A. bisulcatus* was the most potent neurotoxin, resulting in complete paralysis in four of five pigs after 5 days of treatment, and in the last pig after 3 weeks of treatment (Panter et al. 1996). In pigs fed selenate, three of five developed complete paralysis, and one pig developed posterior paralysis after 4–21 days of treatment. Although D,L-selenomethionine resulted in the greatest incidence of selenosis, it was the least potent neurotoxicant, resulting in posterior paralysis in two of five pigs after 9 and 24 days of treatment; the pigs that did not develop paralysis were fed D,L-selenomethionine for approximately 31 days. The form of selenium in *A. bisulcatus* is unknown, although Panter et al. (1996) indicate that it is nonprotein.

It has long been believed that the blind staggers syndrome in livestock results from consumption of plants high in selenium (100–10,000 mg selenium/kg plant) (Rosenfeld and Beath 1964). These plants, which include *A. bisulcatus*, are known as selenium-indicator plants. “Blind staggers” is characterized by impaired vision, aimless wandering behavior, reduced consumption of food and water, and finally paralysis and death (Rosenfeld and Beath 1964; Shamberger 1986). Trembling of the skeletal muscles was observed in steers fed sodium selenite mixed in the feed at doses between 0.6 and 1.1 mg selenium/kg/day (Maag et al. 1960). At necropsy, two of six steers exhibited neuronal degeneration of the cerebral and cerebellar cortices. However, more recent studies in which cattle were treated with known amounts of selenium have not replicated these effects, and it is likely that “blind staggers” is not solely the result of selenium toxicity, but may also be attributable to other unidentified causes. For example, treatment of 20 steers with selenomethionine or selenite in food at doses up to 0.808 mg selenium/kg/day for 120 days produced symptoms of selenosis (hoof lesions), but did not produce any

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neurological signs associated with “blind staggers” or any treatment-related changes in the histology of the central nervous system (O’Toole and Raisbeck 1995).

Neurological effects have also been reported for mice after acute or intermediate exposures to selenium. A single oral dose of selenium dioxide dissolved in water given to mice at 1/10th the LD₅₀ (1.7 mg/kg) caused moderate reductions in alertness, spontaneous activity, touch response, muscle tone, and respiration. Pentobarbital sleeping time was also significantly increased, and there was moderate hypothermia (Singh and Junnarkar 1991). Brain tissue from male BALB/c mice administered sodium selenite or seleno-L-methionine in drinking water at 0, 1, 3, or 9 ppm selenium (sodium selenite: 0.03, 0.24, 0.58, or 1.34 mg selenium/kg/day; seleno-L-methionine: 0.03, 0.26, 0.63, or 1.96 mg selenium/kg/day) for 14 days was examined for changes in the concentrations of norepinephrine (NE), dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), serotonin (5-HT), and 5-hydroxyindolacetic acid (5-HIAA) (Tsunoda et al. 2000). Treatment with seleno-L-methionine produced no significant changes in the concentrations of any of the neurotransmitters or their metabolites. DOPAC, DA, and HVA were increased in the striatum of mice receiving 3 or 9 ppm selenium as selenite. The increase was significant at both concentrations for DOPAC and at 3 ppm (but not 9 ppm) for HVA, but was not significant at either concentration for DA. No changes were observed for levels of NE, 5-HT, or 5-HIAA levels in any brain region of mice treated with sodium selenite.

Exposure of female BALB/c mice to 0.21 mg selenium/kg/day for 6 months from diets containing selenium as sodium selenite resulted in significant changes in behavior during open field testing (Boylan et al. 1990). Open field testing measures the arousal level of small rodents and can differentiate between fear-related behavior and general arousal. Mice receiving excessive selenium had reduced sniffing behavior and exhibited greater activity entering more squares, and more interior squares than mice receiving normal selenium diets. These behaviors are indicative of a general state of arousal rather than fear-motivated activity.

No studies were located concerning neurological effects in humans or experimental animals following oral exposure to selenium sulfide or disulfide.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects following oral exposure to selenium or selenium compounds for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding adverse effects on human reproduction following oral exposure to elemental selenium or to selenium compounds. Associations between high seminal plasma selenium and impaired sperm count or motility have been inconsistently observed in humans (Bleau et al. 1984; Hansen and Deguchi 1996; Roy et al. 1990). A 120-day double blind experimental study found no adverse changes in sperm indices or reproductive hormone in men (20–45 years old) who consumed a controlled diet of foods naturally high or low in selenium (Hawkes and Turek 2001). Eleven subjects were fed a diet that provided 0.0006 mg selenium/kg/day for the first 21 days of the study, followed by diets providing 0.0002 mg selenium/kg/day (6 subjects) or 0.004 mg selenium/kg/day (5 subjects) for 99 days. Semen quality (sperm concentration, semen volume, sperm total number, fraction motile sperm, percent progressive sperm, mean forward velocity, and various sperm morphology parameters), reproductive hormone levels (serum testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone), and thyroid hormone levels (serum T₃ and TSH) were evaluated during weeks 3 (baseline values), 8, and 17 (ending values).

Selenium levels in blood plasma began to change within 3 days of starting the low- and high-selenium diets and progressively continued throughout the study (Hawkes and Turek 2001). By week 17, mean plasma selenium concentrations had increased by 109% in the high-selenium group and decreased by 38.5% in the low-selenium group. A similar pattern of changes occurred in seminal plasma selenium, although selenium levels in sperm did not change significantly in either group. Mean sperm motility was significantly different in the low-selenium subjects and high-selenium groups at week 13, but not at weeks 8 or 17. The fraction of motile sperm increased an average of 10% in the low-selenium group by week 13, and was essentially the same as the baseline value at week 17. Sperm motility decreased an average of 32% in the high-selenium group at week 13, and ended 17% lower than baseline value at week 17. ANOVA showed a significant main effect of dietary selenium on sperm motility, as well as a significant selenium x time interaction, indicating that the group responses diverged over time. Baseline and ending motile sperm fractions in the high-selenium group were 0.588 ± 0.161 and 0.488 ± 0.193 , respectively; $\geq 50\%$ motility is considered normal (FDA 1993). The decrease in sperm motility in the high-selenium group cannot be clearly attributed to selenium because the effect was not consistent over the duration of exposure, is unlikely to be adverse because it is at the low end of the normal range, and is not accompanied by any significant changes in other indices of sperm movement (progression or forward velocity), or sperm numbers or morphology. Additionally, there were no effects of selenium on serum

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levels of reproductive hormones, and changes in thyroid hormones, which could affect sperm function, were not outside normal ranges (see Endocrine Effects in Section 3.2.2.2).

A nonsignificant increase in spontaneous abortions (relative risk [RR]=1.73; 95% CI=0.62–4.80) was reported among births in the municipality of Reggio Emilia, Italy, where women had been exposed to drinking water containing 7–9 ug/L levels of selenium (as selenate, reported estimated intake 10–20 ug/day) between 1972 and 1988 (Vinceti et al. 2000a). This study is limited by a level of selenium in water that is not considered high, lack of data on selenium status, and insufficient information on confounding variables. Selenium deficiency has been implicated as a risk factor for recurrent miscarriage in humans (Al-Kunani et al. 2001; Barrington et al. 1996, 1997; Güvenc et al. 2002; Kumar et al. 2002).

Data from animal studies suggest that exposure to excessive selenium has adverse effects on testosterone levels and sperm production and increases the percentage of abnormal sperm (El-Zarkouny et al. 1999; Kaur and Parshad 1994; NTP 1994). A significant reduction (49%) in serum testosterone levels was reported for New Zealand white rabbits gavaged with 0.001 mg selenium/kg/day as sodium selenite once a week for 6 weeks (El-Zarkouny et al. 1999). The percentage of spermatozoa without an acrosome was also increased in treated rabbits compared with controls, but the difference was not significant. Sperm motility, ejaculate volume, sperm concentration, and total sperm output were all reduced by selenium treatment, but statistical analysis of these data was not presented.

Exposure of Wistar rats to 0.234 mg selenium/kg/day as sodium selenite in water produced testicular hypertrophy (Turan et al. 1999a). A dose-related increase in abnormal sperm and a decrease in live sperm were observed in wild-caught rats exposed to selenite in the diet at 0.1 and 0.2 mg selenium/kg/day (Kaur and Parshad 1994). The percentage of abnormal sperm was 3.9% at 0.1 mg/kg/day and 24.6% at 0.2 mg/kg/day. The abnormalities observed were principally in the midpiece region of the sperm, the region that contains a selenoprotein (Sunde 1990). Decreased sperm counts were observed in rats provided with selenate or selenite in drinking water for 13 weeks at a dose of 0.29 mg selenium/kg/day for selenate and a dose of 0.17 mg selenium/kg/day for selenite (NTP 1994). Effects on sperm were not observed in mice treated with selenate or selenite in the drinking water at doses up to 5.45 mg selenium/kg/day for selenate or up to 3.31 mg selenium/kg/day for selenite (NTP 1994). The administration of 1.05 mg selenium/kg/day as potassium selenate to rats in drinking water for 1 year did not affect male fertility (Rosenfeld and Beath 1954), and the administration of 0.57 mg selenium/kg/day as sodium selenate for three generations did not reduce male fertility in mice (Schroeder and Mitchener 1971b). A short-term reproductive study of the effects of sodium selenate in drinking water on rats at

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doses (0.418 mg selenium/kg/day) that produced signs of systemic toxicity did not cause any increase in sperm abnormalities or lesions of the testis or epididymis (NTP 1996). Selenium administered in the diet or in drinking water over short exposure periods (e.g., 1 month) does not appear to affect the fertility of female animals unless the intake is sufficiently high to cause general toxicity (Nobunaga et al. 1979). Despite a small increase in the number of abnormal length estrous cycles, Nobunaga et al. (1979) found no adverse effect on the fertility of female mice from administration of sodium selenite at doses of 0.34 mg selenium/kg/day in drinking water for 30 days before mating and for 18 days during pregnancy. On the other hand, chronic exposure of mice and rats to otherwise nontoxic doses has been shown to reduce fertility and to reduce markedly the viability of the offspring of pairs that are able to conceive (Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b).

A study of supplementation of female pigs with 0.1 or 0.3 ppm selenium (doses not available) administered as a selenium-enriched yeast or sodium selenite in the diet, from 60 days before breeding until weaning found no adverse effects on reproductive performance (measured by number of offspring) or growth (Mahan and Kim 1996). In another study of the effect of selenium on fertility in pigs, females fed sodium selenite at 0.4 mg selenium/kg/day from 8 weeks of age exhibited reduced rates of conception and also produced offspring with significantly reduced birth weight and weaning weights in the first and second litters (Wahlstrom and Olson 1959b). An altered menstrual cycle was reported in monkeys administered 0.08 mg selenium/kg/day as L-selenomethionine for 30 days (Cukierski et al. 1989).

Vaginal cytology of female rats provided with drinking water containing selenate or selenite indicated that the rats spent more time in diestrus and less time in proestrus and estrus than the controls (NTP 1994). This effect occurred following treatment with 0.31 mg selenium/kg/day as selenate or 0.86 mg selenium/kg/day as selenite. The animals in these studies were not mated, so it is not known if the effects on the estrous cycle had any effect on fertility. Effects on the estrous cycle were not observed in mice treated with selenate or selenite in the drinking water at doses up to 7.17 mg selenium/kg/day for selenate, or at doses up to 3.83 selenium/kg/day for selenite (NTP 1994).

In a three-generation reproduction study, selenium administered as sodium selenate (0.57 mg selenium/kg/day) in the drinking water of breeding mice produced adverse effects on reproduction (Schroeder and Mitchener 1971b). The most notable observed effects included the failure of about half of the F3 generation pairs to breed successfully. In a two-generation study using rats, selenium administered as potassium selenate had no effect on reproduction at a dose of 0.21 mg selenium/kg/day for 1 year; however, decreased fertility and pup survival were noted at 1.05 mg selenium/kg/day (Rosenfeld and

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Beath 1954). At 0.35 mg selenium/kg/day for 1 year, the number of young successfully reared by the females was reduced by 50%, and the body weight of the females was approximately 20% less than that of the control females (Rosenfeld and Beath 1954).

A short-term reproductive study of the effects of sodium selenate in drinking water on rats reported some female reproductive toxicity (reduced corpora lutea, reduced implants per litter, shorter estrous cycle), but only at doses (0.418 mg selenium/kg/day) that produced signs of severe maternal toxicity, including a large reduction in water consumption (NTP 1996).

In a review of selenium poisoning in domestic animals, Harr and Muth (1972) noted a decreased conception rate and an increased fetal resorption rate in cattle, sheep, and horses fed diets naturally containing organic selenium compounds at 25–50 mg selenium/kg diet. Assuming that large animals consume an amount of food equal to about 2–3% of their body weight daily, the doses would have been approximately 0.5–1.5 mg selenium/kg/day. These levels of selenium also produced other signs of toxicity, including hair loss, lameness, and degeneration and fibrosis of the heart, liver, and kidneys. In a case control study of 136 Holstein cows from four herds, an association of cystic ovaries with blood selenium concentrations >108 ng/mL was found (Mohammed et al. 1991). The concentration of progesterone in the milk was significantly higher in the controls than in the cows receiving selenium supplementation, but no information on the selenium dose was presented. No change in estrus cycle length, estrus behavior, progesterone, or estrogen profiles or pregnancy rate was observed in a study of the reproductive response of ewes fed alfalfa pellets containing sodium selenate (24 ppm selenium) or *A. bisulcatus* (29 ppm selenium) as a selenium source for 88 days, from >52 days before pregnancy up to day 28 of gestation (Panter et al. 1995). Doses could not be calculated as food consumption was not listed, and the paper states that the food supply was limited to match that of the group with the lowest intake.

The highest NOAEL value for reproductive effects following intermediate oral exposure to sodium selenite and all reliable LOAEL values for reproductive effects following intermediate or chronic oral exposure to selenium compounds other than selenium sulfide are recorded in Table 3-2 and plotted in Figure 3-2.

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3.2.2.6 Developmental Effects

No studies have demonstrated that selenium or its compounds are teratogenic in humans. Robertson (1970) reported on the outcome of pregnancies in a laboratory in which workers handled sodium selenite. Of the five pregnancies, four ended in spontaneous abortion and one resulted in an infant with bilateral clubfoot. The urinary selenium levels in all subjects were similar to those in other individuals living in the same area. The limited number of cases, possible exposure to other toxic agents, and other confounding factors leave the relationship between sodium selenite and developmental effects inconclusive.

No significant increase in spontaneous abortions (RR=1.73; 95% CI=0.62–4.80) was reported among births in the municipality of Reggio Emilia, Italy, where women had been exposed to drinking water containing 7–9 µg selenium/L (as selenate) between 1972 and 1988 (Vinceti et al. 2000a). Body weight and length at birth were similar in infants of exposed and unexposed women, and no significant increase in the prevalence of congenital abnormalities was found for 353 infants of exposed mothers compared with the 14,481 births among unexposed women. This study is limited by a level of selenium in water that is not considered high, lack of data on selenium status, and insufficient information on confounding variables.

Zierler et al. (1988) performed a case control study of 270 children born in Massachusetts with severe congenital heart disease and 665 controls randomly selected from birth certificates. The study compared the selenium concentrations in the public drinking water supply used by the mothers close to the time of conception to the selenium concentrations in the water consumed by the controls. The results indicated that selenium exposure via drinking water was associated with beneficial effects, particularly a reduction in the risk of congenital heart defects (cono-truncal defects, ventricular septal defects, coarctation of the aorta, and patent ductus arteriosus), but many variables are unknown, including other possible confounders (no adjustment for age, parity, tobacco, alcohol, drug use, or socioeconomic status), other sources of selenium in the mothers' diet and environment, the amount of drinking water consumed, and the selenium concentrations in the water during the first trimester.

Excess selenium is a demonstrated teratogen in birds. However, there is no clear evidence linking selenium exposures to teratogenic effects in mammals. Several studies have documented the sensitivity of chick embryos to selenium poisoning. Hatchability of eggs is reduced by dietary levels of organic selenium in grain that are too low to cause toxicity in other farm animals. The eggs are fertile but often

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produce grossly deformed embryos lacking eyes and beaks and having deformed wings and feet (Franke and Tully 1935; Franke et al. 1936; Gruenwald 1958; Palmer et al. 1973). Deformed embryos have also been produced by injection of aqueous sodium selenite or sodium selenate into the air cell of the normal, fertile eggs of chickens (Franke et al. 1936; Khan and Gilani 1980). The incidence of malformation among coot, duck, stilt, and grebe embryos from eggs of birds ingesting plant and other food from irrigation drainwater ponds in the San Joaquin Valley of California was much higher than expected (10–42%, depending on the species, versus <1% based on data from other areas) (Ohlendorf et al. 1986a, 1988). Selenium concentrations in these ponds were >0.3 mg/L.

The consumption of naturally high seleniferous diets by sheep (Rosenfeld and Beath 1964) and cattle (Dinkel et al. 1963) may interfere with normal fetal development and produce malformations. Malformations were associated with alkali disease and occurred at dietary levels that produced other toxic manifestations, but it is not clear if these reports took into account consumption of other toxic range plants. The specific selenium compound or compounds possibly associated with livestock developmental toxicity have not been identified. No change in the outcome of pregnancy was observed in a study of the reproductive response of ewes fed alfalfa pellets containing sodium selenate (24 ppm selenium) or *A. bisulcatus* (29 ppm selenium) as a selenium source for 88 days, from >52 days before pregnancy up to day 28 of gestation (Panter et al. 1995). All lambs appeared normal, and there was no significant difference in the number or weight of lambs born to treated and control ewes. Doses could not be calculated, as food consumption was not listed, and the paper states that the food supply was limited to match that of the group with the lowest intake.

In an intermediate-duration study, an increased number of deaths between birth and weaning, reduced birth weight, and reduced body weight at weaning were observed in offspring of pigs fed selenite at 0.4 mg/kg/day for an unstated period of time (Wahlstrom and Olson 1959b). Treatment of 15 pregnant cows with diets containing 0.25 (control), 6, or 12 ppm selenium (0.005, 0.135, or 0.265 mg Se/kg/day) as sodium selenite beginning at 80–110 days gestation and continuing for 3 months resulted in no abnormalities among the offspring apart from one calf in the 12 ppm group that was born weak and subsequently died (Yaeger et al. 1998). This calf had myocardial lesions similar to those described for selenium toxicosis and had markedly elevated hepatic selenium levels, although selenium levels in blood and hair of this calf and its dam were lower than average for the 12 ppm group.

In studies of laboratory mammals, the administration of inorganic selenium compounds at levels that are not maternally toxic has not produced terata (Bergman et al. 1990; Chiachun et al. 1991; Ferm et al. 1990;

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NTP 1996; Poulsen et al. 1989; Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b; Thorlacius-Ussing 1990). Ferm et al. (1990) administered a single dose of sodium selenate, sodium selenite, or L-selenomethionine (0, 1.8, 2.2, 2.7, 4.0, 5.0, or 5.9 mg selenium/kg/day) to pregnant Syrian hamsters on gestation day 8. Pathological examination of the fetuses on day 13 showed that the percentage of abnormal litters was significantly increased at doses of ≥ 2.7 mg/kg. Encephalocele was the major malformation noted, and incidences were as follows: 0/71 controls; 4/55 (7.3%) at 1.8 mg/kg; 1/49 (2%) at 2.2 mg/kg; 7/66 (10.6%) at 2.7 mg/kg; 15/70 (21.4%) at 4 mg/kg; 9/38 (23.7%) at 5 mg/kg; and 6/16 (37.5%) at 5.9 mg/kg. Nobunaga et al. (1979) found that administration of sodium selenite in drinking water at 0.34 mg selenium/kg/day for 30 days before mating and for 18 days during pregnancy slightly, but significantly, reduced fetal growth in mice. However, there was no effect on fetal growth in the same study at a dose of 0.17 mg selenium/kg/day. A short-term developmental study (from gestation day 6 until birth) of the effects of sodium selenate in drinking water on rats produced some developmental toxicity (decreased number of live births, reduced pup weight, increased gestation period), but only at doses (0.418 mg selenium/kg/day) that produced signs of severe maternal toxicity including a large reduction in water consumption (NTP 1996). Selenium administered as potassium selenate in drinking water to male and female rats at a dose of 1.05 mg selenium/kg/day for 1–8 months for two successive generations did not cause congenital malformations (Rosenfeld and Beath 1954). Similarly, administration of 0.57 mg selenium/kg/day as sodium selenate in the drinking water of breeding mice for three generations did not have teratogenic effects, although there was an increased incidence in fetal deaths, and a high proportion of the surviving offspring were runts (Schroeder and Mitchener 1971b).

Poulsen et al. (1989) demonstrated that pigs exposed to 42.4 mg/day of selenium as sodium selenite in feed throughout pregnancy produced normal litters, with no adverse effect on piglet survival, litter size, or body weight at birth. Body weights of the pigs during pregnancy were not provided, and therefore, mg/kg/day doses could not be calculated. Body weight gains of pigs fed selenium as selenite at a dose of 0.4 mg selenium/kg/day after weaning (duration not specified) were reduced (Wahlstrom and Olson 1959a). The reduction in body weight gain was greater among pigs from dams not fed selenium during gestation and lactation compared to pigs fed selenium (0.4 mg/kg/day) during gestation and lactation. Without providing data, the study authors indicated that there was a greater loss of pigs at birth and during lactation from sows fed selenium, which may have eliminated susceptible pigs.

In a teratology study of long-tailed macaques, no gross abnormalities or growth retardations were observed in fetuses from mothers administered L-selenomethionine at levels of 0.003, 0.025, 0.15, or

0.30 mg selenium/kg/day on gestational days 20–50 (10 animals per group); the mid and high doses were maternally toxic (Tarantal et al. 1991).

The highest NOAEL value and all reliable LOAEL values for developmental effects following intermediate or chronic oral exposure to selenium compounds are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

Early studies reporting that selenium was carcinogenic in mammals after being provided as seleniferous corn or wheat in the diet (Nelson et al. 1943), as sodium selenite or sodium selenate in drinking water (Schroeder and Mitchener 1971a), or as sodium selenate in the diet (Volgarev and Tscherkes 1967) were flawed. The majority of subsequent studies of humans and animals have revealed no association between selenium intake and the incidence of cancer (Azin et al. 1998; Beems 1986; Coates et al. 1988; Harr et al. 1967; Ma et al. 1995; Menkes et al. 1986; Ratnasinghe et al. 2000; Thompson and Becci 1979; Vinceti et al. 1995; Virtamo et al. 1987) or a clear chemopreventive association (Birt et al. 1982; Clark et al. 1996a, 1999; Finley et al. 2000; Ip 1981, 1983; Ganther and Lawrence 1997; Ip and Lisk 1995; Ip et al. 1996, 1997, 1998, 2000a, 2000b; Jiang et al. 1999; Ma et al. 1995; Medina and Shepherd 1981; Moyad 2002; Overvad et al. 1985; Schrauzer et al. 1976, 1977; Shamberger et al. 1976; Soullier et al. 1981; Thompson and Becci 1980; Woutersen et al. 1999; Yoshizawa et al. 1998). Some epidemiological and experimental evidence suggests that selenium exposure, under certain conditions, may contribute to a reduction in cancer risk (Clark et al. 1996a, 1999; El-Bayoumy 2001; Ganther 1999; Moyad 2002; Spallholz 2001; Yoshizawa et al. 1998), and the chemopreventive potential of supplemental selenium is currently under research (Clark et al. 1999; Duffield-Lillico et al. 2002; Reid et al. 2002).

The only selenium compound that has been shown to be carcinogenic in animals is selenium sulfide (NTP 1980c), although there is also some evidence for carcinogenicity due to ethyl selenac (selenium diethyldithiocarbamate) (Innes et al. 1969; NCI 1968). These compounds are very different chemically from the organic and inorganic forms found in foods and the environment. Human dietary studies generally do not identify the selenium form specifically; both organic (from grains and other plant and animal products) and inorganic (from drinking water) forms are ingested. Animal bioassays in which selenium was administered as sodium selenate, sodium selenite, or organic forms of selenium have all shown similar negative results.

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Excess incidence of melanoma was reported for a cohort of 2,065 individuals that were exposed to 7–9 µg/L levels of selenium as selenate in the municipal water supply in Reggio Emilia, Italy from 1972 until 1988 (Vinceti et al. 1998). Eight individuals among the exposed cohort developed melanoma compared with 128 in the remainder of the municipal population (total number of individuals not given). The standardized mortality ratios (SMRs) were 5.0 (95% CI=1.6–12.0) for males and 3.2 (95% CI=1.0–7.7) for females. The authors estimate the general dietary intake of selenium in the area to be 45–50 µg/day and the excess selenium supplied in the contaminated tap water to be 10–20 µg/day. However, the study is limited by the fact that no individual measurements of selenium exposure were made, and individuals were classed as exposed or unexposed depending on their place of residence. The lack of data on selenium status indicates that the study found a correlation but not causation. Other limitations include a water level of selenium that is not generally considered to be high and insufficient information on confounding variables.

A study of the effects of nutritional supplementation with selenium found a significant reduction in overall cancer mortality and in the incidence of lung (RR=0.54, 95% CI=0.3–0.98, p=0.04), colorectal (RR=0.42, 95% CI=0.18–0.95, p=0.03), and prostate (RR=0.37, 95% CI=0.18–0.71, p=0.003) cancer (Clark et al. 1996a, 1999). The original intent of the study was to assess the effects of selenium supplementation on nonmelanoma skin cancer. Patients with a history of skin carcinoma (1,312 individuals) were randomized into two groups; one group received a selenium supplement of 200 µg/day, and the other received a placebo. Groups were treated for an average of 4.5 years and followed for an average of 6.5 years. Supplementation produced no difference in skin cancer incidence; however, secondary end point analyses of the data found a protective effect for selenium for the cancers described above. A reanalysis of the lung cancer data added eight cases to the selenium-treated group, four cases to the placebo group, and increased follow-up to 7 years (Duffield-Lillico et al. 2002; Reid et al. 2002). Selenium supplementation did not reduce lung cancer incidence in the full population (RR=0.70, 95% CI=0.40–1.21, p=0.18; hazard ratio [HR]=0.74, 95% CI=0.44–1.24, p=0.26), although a nominally significant decrease was observed among subjects with baseline plasma selenium concentrations in the lowest tertile (HR=0.42, 95% CI=0.18–0.96, p=0.04). The analysis for the middle and highest tertiles of baseline selenium level showed HRs of 0.91 and 1.25, suggesting that there was a trend toward a reduction in risk of lung cancer with selenium supplementation.

Supporting evidence for an antiprostata cancer effect of selenium was obtained for a nested case-control design within the Health Professional Follow-up study (Yoshizawa et al. 1998), which found that higher

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prediagnostic selenium levels were associated with reduced prostate cancer incidence. This study included 33,737 male health professionals aged 40–75 years who provided toenail clippings in 1987. The cohort was assessed by questionnaire for incidence of new cases of prostate cancer from 1989 to 1994. Higher levels of selenium in toenail clippings were significantly associated with a reduced risk of prostate cancer. After controlling for factors such as a family history of prostate cancer, body mass index, calcium intake, lycopene intake, saturated fat intake, vasectomy, and geographical region, the odds ratio (OR) was 0.35 (95% CI=0.16–0.78, *p* for trend=0.03). Studies of selenium supplementation have generally shown a reduction in prostate cancer risk only in individuals who had lower levels of baseline plasma selenium, whereas subjects with normal or higher levels did not benefit and may have an increased risk for prostate cancer (Moyad 2002).

Epidemiological studies that focused on the selenium concentration of forage crops as an indicator of available dietary selenium indicated an inverse association between selenium levels and cancer occurrence, with few exceptions. In the United States, male mortality due to cancer of the tongue, esophagus, stomach, intestine, rectum, liver, pancreas, larynx, lungs, kidneys, and bladder was significantly lower in states with high selenium levels in forage crops (concentrations in excess of 0.10 mg selenium/kg) (Shamberger et al. 1976). For females in states with high selenium levels, significantly lower cancer death rates were found for cancer of the esophagus, stomach, intestine, rectum, liver, pancreas, lungs, bladder, thyroid, breast, and uterus (Shamberger et al. 1976). Only male and female mortality due to cancer of the skin and eye, male mortality due to cancer of the lip and aleukemic leukemia (a deficiency or absence of leukocytes in the blood due to leukemia), and female mortality due to dermal melanoma were associated with high selenium levels in forage crops. Many of the high selenium areas are in the southwestern portion of the United States, and therefore, exposures to ultraviolet light may have contributed to the skin cancers observed in these areas (Shamberger et al. 1976). In a comparison of selenium intake and cancer mortality rates in different countries, Schrauzer et al. (1977) detected a cancer chemopreventive association between the selenium content of the diet and age-corrected cancer mortality from leukemia and cancers of the intestine, rectum, breast, ovary, prostate, lung, pancreas, skin, and bladder.

In a case control study of lung cancer patients, Menkes et al. (1986) found that the risk of lung cancer was not associated with serum selenium levels (0.113 and 0.110 mg selenium/L in cases and controls, respectively), but was significantly increased with decreasing serum levels of vitamins A and E. The study authors suggested that high serum selenium levels were significantly associated with an increased incidence of squamous cell carcinoma as compared to other cellular tumor types, but the statistical

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analysis used was flawed. In a region of China with high rates of stomach cancer and low intake of several micronutrients (selenium not specifically stated), an intervention trial in 29,584 adults for 5.25 years demonstrated a 21% decrease in stomach cancer in the randomly selected group receiving a nutritional supplement of beta carotene (15 mg/day), vitamin E (30 mg/day), and selenium (50 µg selenium/day as selenium yeast) (Blot et al. 1993). However, because the three nutrients were given in combination to a nutritionally deficient population, it is not possible to determine what part of this effect (if any) was due to selenium.

Low serum selenium levels have been associated with an increased incidence of cancer in some prospective epidemiological studies (Salonen et al. 1984, 1985; Willet et al. 1983). In the United States, Willet et al. (1983) found that the risk of cancer for subjects in the lowest quintile (fifth) of serum selenium concentrations (<0.115 mg selenium/L) was twice that of subjects in the highest quintile (>0.154 mg selenium/L). In Finland, Salonen et al. (1985) found the risk of fatal cancer for subjects in the lowest tertile (third) of serum selenium concentrations (<0.047 mg selenium/L) was 5.8 times higher than that of the remaining subjects. Mean serum selenium levels in Americans (0.129 mg selenium/L cases; 0.136 mg selenium/L controls) (Willett et al. 1983) are more than twice the mean serum selenium levels in the Finns (0.0505 mg selenium/L for cases; 0.0543 mg selenium/L for controls) (Salonen et al. 1984). Although the age-specific risk of fatal cancers in the two populations cannot be calculated from the data reported, the overall incidence of cancer in the 4-year Finnish study was less than half that in the 5-year U.S. study. In addition, other prospective studies of Americans have found no correlation between fatal cancer and blood selenium concentrations (Coates et al. 1988). Thus, one may not be able to predict relative cancer risks with serum selenium levels in one population based on data from another population.

A 9-year prospective follow-up study was conducted by Virtamo et al. (1987) on a group of men in Finland. At the beginning of the study, blood samples were taken as part of a study of coronary heart disease and other atherosclerotic diseases. Cancer data were collected from central registries for the years 1976 through 1983. The results indicated no association between low serum selenium levels (<0.045 mg selenium/L) and an increased risk of cancer. Evidence suggests that combined dietary deficiencies of vitamin E and selenium may be associated with increased cancer risk (Salonen et al. 1985).

Epidemiological studies of breast cancer have found inverse correlations, positive correlations, and no correlations between tissue selenium concentrations and cancer incidence (recently reviewed by Garland et al. 1993). In a case control study of plasma selenium and breast cancer in which the controls had benign breast disease, a preventive effect of selenium was found only among individuals who had higher

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plasma selenium and were not taking selenium supplementation (Hardell et al. 1993). This effect was significant (odds ratio 0.38) at a serum selenium concentration range of 0.08–0.09 mg/L in women 50 years old or more. GPX activity in erythrocytes was not found to be a marker for the risk of breast cancer. A case control study of 162 cases of breast cancer in Dutch women did not find a significant difference in dietary, plasma, erythrocyte, or toenail selenium between cases and 529 controls when multivariate-adjusted odds ratios were calculated. Dutch women have lower selenium intake than women in the United States and one of the highest incidences of breast cancer in Western Europe. The authors of this study surmised that other studies reporting an inverse relationship between selenium levels and breast cancer may be seeing an effect of the cancer (e.g., decreased uptake of selenium or anorexia), rather than lower selenium level contributing to the development of cancer (van't Veer et al. 1990). Similarly, a large prospective study of 434 cases in the United States found no correlation between selenium content in nails, established as a long-term marker of selenium (Hunter et al. 1990a), and breast cancer (Hunter et al. 1990b). It is interesting to note that a more recent investigation of the same cancer cases found an inverse correlation between vitamin A (retinoids) in the diet and breast cancer (Hunter et al. 1993). Retinoids are believed to have chemopreventive activity (Clausen et al. 1989; Hunter et al. 1993). Although the data as a whole for breast cancer and tissue selenium concentrations do not support a clear chemopreventive effect for selenium, it is possible that very high selenium concentrations or very low selenium concentrations outside the ranges observed in these studies could play a role in human cancer risk (Garland et al. 1993).

There were several inadequacies in the early studies that reported carcinogenic effects in animals following oral administration of selenium-containing compounds. Nelson et al. (1943) (also reported as Fitzhugh et al. 1944) administered naturally seleniferous corn or wheat diets containing 5, 7, or 10 mg selenium/kg diet (0.25, 0.35, or 0.50 mg selenium/kg/day) to female rats for 2 years. Selenium administration produced high mortality (69%) in all treatment groups by the end of the first 12 months, and the first tumors appeared after 18 months of treatment. Tumors developed only in animals with cirrhotic livers, and the tumors were reported to be nonmalignant. The possible contribution of overt hepatotoxicity to the development of liver tumors is not known. The incidences of tumors in the surviving animals in the three dose groups were 6/25, 3/21, and 2/7, respectively. The investigators had difficulty discerning malignant from nonmalignant tumors, and most animals had died of cirrhosis of the liver before the appearance of liver tumors. These difficulties cast doubt on the conclusion of the investigators that selenium induced tumor formation in these rats.

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A statistically significant increase was reported in the incidence of all tumors and malignant tumors in rats administered 0.28–0.42 mg selenium/kg/day as sodium selenite or sodium selenate in drinking water for a lifetime (Schroeder and Mitchener 1971a). Not all autopsied animals were examined histologically, however, and high mortality in all groups occurred as a result of a virulent pneumonia epidemic that occurred during the study. In addition, the statistical analysis failed to account for the fact that the selenium-treated rats lived longer than did the control rats. Analysis of the incidence of tumors among animals with equal longevities indicates that the incidence of tumors in the selenate-treated rats was not significantly different from that in the controls.

A series of dietary studies assessed the effects of various dietary supplements on selenium tumor induction in male rats (Vologarev and Tschirkes 1967), but the conclusions that can be drawn from these experiments are limited since they did not include controls. Tumors (primarily liver) were found in 10/23 male rats administered sodium selenate in the diet at a dose of 0.34 mg selenium/kg/day for more than 18 months (Vologarev and Tschirkes 1967). The first tumors appeared after 18 months of selenium administration, by which time, 43% of the animals had already died (group started with 40 animals). Tumors were also found in 3/16 male rats administered sodium selenate in the diet at an initial dose of 0.34 mg selenium/kg/day for 6 months, followed by 0.68 mg/kg/day until the animals' death (Vologarev and Tschirkes 1967). In a third group of experiments, no tumors were found in 200 male rats administered sodium selenate in the diet (0.34 mg selenium/kg/day) for 26 months. However, there was very high mortality among these rats, and survival time was 10 months shorter than among the similarly fed animals in the first experiment. The authors noted that an additional 200 male rats were maintained in their laboratory during these experiments and fed stock rations. The life spans of these animals exceeded those used in the experiments and no tumors were found at autopsy.

More recent animal bioassays have failed to demonstrate any association between excessive selenium exposure and carcinogenesis. Chen et al. (2000) reported a significant increase in rat esophageal adenocarcinogenesis in response to supplementation with 0.06 mg selenium/kg/day as sodium selenite for 40 weeks. However, selenium supplementation has generally been shown to significantly inhibit tumors induced by chemicals, viruses, or ultraviolet light (Birt et al. 1982; Finley et al. 2000; Ip 1981, 1983; Ip and Lisk 1995; Ip et al. 1996, 1997, 1998, 2000a, 2000b; Jacobs 1983; Jacobs et al. 1977a, 1977b, 1979, 1981; Jiang et al. 1999; Medina and Shepherd 1981; Overvad et al. 1985; Schrauzer et al. 1976; Soullier et al. 1981; Thompson and Becci 1980; Woutersen et al. 1999). Results following administration of selenium as sodium selenate, sodium selenite, and organic forms of selenium are similar. Additional

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research reviewed in El-Bayoumy (1991, 1995, 1997) indicates that synthetic organoselenium compounds may be more potent cancer preventive agents than selenate, selenite, or the selenoamino acids.

Two sources reported the results of a study of rats administered sodium selenate or sodium selenite in the diet for a lifetime (Harr et al. 1967; Tinsley et al. 1967). A vehicle control and two positive control groups (administered a known hepatocarcinogen, *N*-2-fluorenyl-acetamide [FAA]) were included. Mortality was high in the highest dose group (0.8 mg selenium/kg/day), and therefore, selenium administration was discontinued. Longevity was reduced in animals fed 0.4 mg selenium/kg/day, but not in the animals administered lower doses. Of the original 1,437 experimental animals, 1,126 were necropsied. Half of the 88 FAA-fed rats developed neoplasms, half of which were hepatic carcinomas, indicating that the strain of rat and dietary conditions were compatible with the development of hepatic carcinogenesis. The incidence of cancer of all types in the necropsied control rats (11 out of 482, or 2.3%) was somewhat higher than the incidence of cancer in the selenium-treated animals that were necropsied (9 out of 553, or 1.6%). A statistical analysis of the data from this study was not reported. Although the reduced longevity of animals administered 0.4 mg selenium/kg/day might have prevented the observation of some late-developing cancers, the large number of rats necropsied, the end points examined, and the doses administered provide credible evidence of the lack of carcinogenic potential of sodium selenate or selenite.

Mice were fed tortula yeast diets containing up to 1.0 mg selenium/kg diet (equivalent to 0.13 mg selenium/kg body weight/day) as sodium selenite for 2 weeks prior to a single application of 0.125 mg 7,12-dimethylbenz[a]anthracene (DMBA) to the skin or repeated daily applications of 0.25 mL of a 0.03% solution of benzo[a]pyrene in acetone for 27 weeks (Shamberger 1970). The highest dose of selenite used, 0.13 mg selenium/kg/day, significantly decreased the number of tumors induced by both aromatic compounds. No significant increase was found in the incidence of spontaneous tumors in mice following administration of 3 mg selenium/L in drinking water as either sodium selenite or sodium selenate for a lifetime (Schroeder and Mitchener 1972). This level corresponds to doses of 0.31–0.34 mg selenium/kg/day for the males and 0.42 mg selenium/kg/day for the females. The single dose administered, however, might not have been the maximal dose that could be tolerated. There were 7% more malignant tumors in the selenium-treated animals (13 out of 88 sectioned, or 15%) than in the controls (10 out of 119 sectioned, or 8%), but the difference was not statistically significant. The forms of selenium administered did not influence the incidence of tumors. In this study, only 88 out of 211 selenium-treated animals and 109 out of 209 control animals were examined histologically.

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The only selenium compound that has been shown to be carcinogenic in animals is selenium sulfide (NTP 1980c), although there is some inconclusive evidence that ethyl selenac may also be carcinogenic (Innes et al. 1969; NCI 1968). A statistically significant increase in hepatomas (0/16 controls; 12/16 treated) was observed in male mice of one strain (C57BL/6 x C3H/Anf)_{F1}) receiving 2 mg selenium/kg as ethyl selenac, but not in male or female mice of another strain (C57BL/6 x AKR)_{F1}) receiving the same dose (Innes et al. 1969; NCI 1968).

Statistically significant increases in hepatocellular carcinomas and adenomas in rats and hepatic carcinomas and adenomas, as well as alveolar/bronchiolar carcinomas and adenomas, in female mice have been observed following chronic oral exposure to selenium sulfide (NTP 1980c). The incidence of hepatocellular carcinomas in rats was 1/50, 0/50, and 15/49 in males and 0/50, 0/50, and 21/50 in females at 0, 3, and 15 mg selenium sulfide/kg/day, respectively. In mice, the incidences of hepatocellular carcinomas and adenomas were 15/50, 14/50, and 23/50 in males, and 0/49, 2/50, and 25/49 in females at 0, 20, and 100 mg selenium sulfide/kg/day, respectively. Selenium sulfide is a pharmaceutical compound used in some antidandruff shampoos and is not administered orally. Because selenium sulfide is not absorbed through the skin, use of shampoos containing this compound should be safe, unless one intentionally consumes the product or has open cuts or sores on the scalp or hands. Chemically, selenium sulfide and ethyl selenac are very different from the organic and inorganic selenium compounds found in foods and in the environment.

In 1975, the International Agency for Research on Cancer (IARC) evaluated the literature relating selenium to carcinogenesis in both humans and animals. The Agency stated that the available data provided no suggestion that selenium is carcinogenic in humans (IARC 1975a), and IARC subsequently assigned selenium to Group 3: not classifiable as to its carcinogenicity to humans (IARC 1987). The forms of selenium considered included sodium selenate, sodium selenite, and the organic forms of selenium contained in plant materials. Separate evaluations of ethyl selenac and methyl selenac assigned them to Group 3, also (IARC 1975a, 1987). According to EPA, selenium is not classifiable as to its carcinogenicity in humans and is rated as Group D (IRIS 2003). The evidence for selenium sulfide, however, is sufficient to classify it as Group B2 (probable human carcinogen) (IRIS 2003).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located concerning death in humans after dermal exposure to selenium or selenium compounds. In a range-finding study using mice dermally exposed to selenium sulfide for a maximum of 17 applications, 8 out of 20 animals died at 714 mg selenium sulfide/kg (NTP 1980a). However, the effects noted in this study were equivocal since there was no indication that the application sites were covered to prevent ingestion. Further, severe skin damage developed, and this may have led to direct systemic absorption of the compound.

3.2.3.2 Systemic Effects

No studies were located concerning respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or other animals following dermal exposure to selenium or selenium compounds.

Dermal Effects. Skin toxicity in humans, notably skin rashes, burns, and contact dermatitis, has been reported for both acute and chronic exposure to selenium fumes and acute exposures to selenium dioxide (Middleton 1947). No effects were detected in a study of eight women exposed daily for 2 weeks to an experimental sunscreen lotion containing up to 0.003 mg/kg/day selenium as L-selenomethionine (Burke et al. 1992a). A case report of a severe allergic skin response following intermediate exposure to sodium selenite (Senff et al. 1988) is discussed under immunological effects. Single topical exposures to selenious acid resulted in purpura, inflammation around hair follicles, and a pustular rash with some ulceration in exposed workers (Pringle 1942). However, these effects may have been due to the caustic effects of the acid. A single case report of hyperpigmentation and hair loss after use of a shampoo containing 1% selenium sulfide was located (Gillum 1996), but a study of the efficacy of an antidandruff shampoo containing 1% selenium sulfide found no adverse effects after 6 weeks of use by 150 individuals (Neumann et al. 1996).

Application of 100 µL of a lotion (oil-in-water emulsion) containing 0.02% selenium as selenomethionine 3 times a week to the shaved backs of mice for 39 weeks did not result in significant dermal effects (Burk

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et al. 1992b). Dermal effects were also not observed in hairless mice treated in the same manner for 49 weeks.

In mice, topical application of selenium sulfide resulted in erythema and skin irritation at 29 mg/kg, acanthosis at 143 mg/kg, and severe skin damage at 714 mg/kg (NTP 1980a).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to selenium or selenium compounds. However, older reports on eye contact with selenium or selenium compounds indicate that acute exposure to selenium dioxide caused ocular and conjunctival irritation, and caused severe pain, lacrimation, blurred vision, and dulled corneas upon contact (Middleton 1947). Brief exposure to clouds of selenium fumes resulted in lacrimation, irritation, and redness of the eyes (Clinton 1947).

No studies were located regarding ocular effects in laboratory animals after dermal exposure to selenium or selenium compounds.

3.2.3.3 Immunological and Lymphoreticular Effects

A 1988 case report describes a female laboratory technician who developed severely pruritic vesicles between the fingers after 6 months of exposure to a medium containing selenium. After 2 years, the severity of the symptoms increased to include eczema on the face and neck, watering eyes, and two asthma attacks within a 2-month period. Sodium selenite or the medium containing selenium were the only positive patch tests (Senff et al. 1988).

No studies were located regarding immunological and lymphoreticular effects in laboratory animals after dermal exposure to selenium or selenium compounds.

No studies were located regarding the following health effects in humans or laboratory animals after dermal exposure to selenium or to selenium compounds:

3.2.3.4 Neurological Effects**3.2.3.5 Reproductive Effects****3.2.3.6 Developmental Effects****3.2.3.7 Cancer**

No studies were located regarding carcinogenic effects in humans after dermal exposure to selenium or selenium compounds.

The results of most animal studies have not indicated that elemental selenium or selenium compounds are carcinogenic when topically applied to the skin of experimental animals (NTP 1980a, 1980b; Shamberger 1970). Several studies indicate that selenium compounds may protect against effects of known dermal carcinogens (polynuclear aromatic hydrocarbons [PAHs] and ultraviolet light). Shamberger (1970) reported that topical application of a solution containing 0.0005% sodium selenide significantly reduced the number of dermal papillomas induced by painting DMBA on the shaved backs of mice. More recently, Burke et al. (1992b) reported orally and topically administered l-selenomethionine decreased ultraviolet burns and skin cancer in albino (BALB:c) and hairless pigmented (Skh:2) female mice.

Only one study was found in which tumor development was reported after topical administration of selenium ointment (Tsuzuki et al. 1960). An unspecified number of mice were exposed to an unspecified amount of ointment containing 2.5, 5.0, 7.5, or 10% elemental selenium 6 days/week for an unspecified period of time by topical administration to hip skin. Tumors developed on the base of the necks of two female mice. Ingestion of the compound was possible because the animals may have licked the ointment. No other details were reported. The study is inconclusive because of the lack of controls, short duration, and inadequate description of the study protocol and results.

The National Toxicology Program (NTP 1980a) conducted a dermal application study of selenium monosulfide. The compound was applied to the skin of groups of 50 male and 50 female Swiss mice at 0, 0.5, or 1.0 mg selenium sulfide/mouse, 3 days/week for 86 weeks. The application sites were not covered; therefore, ingestion of the test compounds was possible. The incidence of tumors in the treated groups did not differ significantly from that in the control group.

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NTP (1980b) also tested Selsun, a prescription dandruff shampoo containing 2.5% selenium sulfide (also a mixture of the mono- and disulfides), for carcinogenic properties. Groups of 50 male and 50 female Swiss mice were dermally exposed to a 0, 25, or 50% solution of Selsun in distilled water 3 days/week for 86 weeks. These doses were equivalent to 0, 0.31, or 0.625 mg selenium sulfide/mouse/day. The incidences of alveolar or bronchiolar adenomas or carcinomas in male mice were significantly increased over vehicle control values, but not over untreated control values. There was no significant effect in female mice. Some ingestion of the compound was possible, because the application sites were not covered. Also, the male mice may have been susceptible to another ingredient in the shampoo (the chemical composition of the shampoo was not reported), or the bioassay may have been too short due to decreased survival to detect a carcinogenic effect in females. Male mice that received dermal application of slightly larger doses of selenium sulfide (NTP 1980a) did not develop significantly more cancers than the controls.

3.2.4 Other Routes of Exposure

Endocrine Effects. Intraperitoneal injection of diabetic rats with sodium selenate has been reported to have insulin-like effects, producing a decrease in plasma glucose concentrations (McNeill et al. 1991). However, it is not clear that this is due to an effect of selenium on insulin metabolism, since food and water consumption were also decreased, and this is likely to have produced the decreased glucose levels.

Neurological Effects. Intraperitoneal injection of selenium (3.0 mg Se/kg as sodium selenite) into male Sprague-Dawley rats produced a significant increase (70%) in dopamine overflow from the striatum (as measured by an implanted dialysis probe) with a concomitant significant reduction in HVA levels (Rasekh et al. 1997). DOPAC levels were not changed. Direct infusion of 10 mM selenium into the striatum also produced a significant increase in dopamine overflow accompanied by slight, but significant decreases in HVA and DOPAC. Direct infusion of 10 mM selenium into the nucleus accumbens also produced a rapid and significant increase in dopamine overflow, but with no changes in DOPAC or HVA concentrations. The selenium induced changes in dopamine overflow were suppressed by the dopamine receptor agonist quinpirole.

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3.3 GENOTOXICITY

Inorganic selenium compounds have been observed to have both genotoxic and antigenotoxic effects. The antigenotoxic effects generally occur at lower selenium exposure levels than the frank genotoxicity. This discussion will focus on genotoxic effects only. *In vitro* studies of the genotoxicity of selenium compounds are summarized in Table 3-4, and *in vivo* studies of the genotoxicity of selenium compounds are summarized in Table 3-5.

Selenium dioxide was found to be mutagenic in both the Ames and the VITO-TOX *Salmonella typhimurium* tests of genotoxicity (van der Lelie et al. 1997).

In general, sodium selenite and sodium selenate have produced mixed results in bacterial mutagenicity test systems (Table 3-4). Sodium selenite induced base-pair substitution mutations using *S. typhimurium* and was also positive in the transformation assay using *Bacillus subtilis* (Kramer and Ames 1988; Nakamuro et al. 1976; Noda et al. 1979). However, negative results have also been reported for sodium selenite both in *S. typhimurium* and the rec assay using *B. subtilis* (Lofroth and Ames 1978; Noda et al. 1979). Sodium selenate, on the other hand, has tested positive in *S. typhimurium* (base-pair substitution) and in the rec assay using *B. subtilis* (Lofroth and Ames 1978; Noda et al. 1979), but has tested negative using the transformation assay in *B. subtilis* (Nakamuro et al. 1976).

Results with mammalian cell systems are also mixed, although sodium selenite is more consistently genotoxic in these systems. Sodium selenite has been observed to induce unscheduled deoxyribonucleic acid (DNA) synthesis (UDS), chromosomal aberrations, and sister chromatid exchange in cultured human fibroblasts (Lo et al. 1978; Ray et al. 1978; Whiting et al. 1980); UDS in Chinese hamster V79 cells (Sirianni and Huang 1983); and chromosomal aberrations in cultured Chinese hamster ovary cells (Whiting et al. 1980). However, sodium selenate induced chromosomal aberrations in Chinese hamster ovary cells (Whiting et al. 1980) and UDS in Chinese hamster V79 cells (Sirianni and Huang 1983), but did not induce chromosomal aberrations in human leukocytes or cultured human fibroblasts (Lo et al. 1978; Nakamuro et al. 1976). A comparison of cytotoxicity and induction of tetraploidy in Chinese hamster V79 cells induced by sodium selenite or its major excretory product trimethylselenonium found that sodium selenite was about 1,000 times more cytotoxic than trimethylselenonium, but that neither compound produced a significant change in mitotic index (Ueda et al. 1997).

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Table 3-4. Genotoxicity of Selenium *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms:				
	Mutation			
<i>Salmonella typhimurim</i>	(Na ₂ SeO ₃)		—	Lofrothand
	(Na ₂ SeO ₄)	NT	+	Ames 1978
<i>S. typhimurim</i>	(SeO ₂)	NT	+	van der Lelie et al. 1997
<i>S. typhimurim</i> TA100	(Na ₂ SeO ₃)	NT	+	Noda et al.
<i>S. typhimurium</i> TA98, TA1537		NT	—	1979
<i>S. typhimurium</i> TA100	(Na ₂ SeO ₄)	NT	+	
<i>S. typhimurium</i> TA98, TA1537		NT	—	
<i>Bacillus subtilis</i> rec assay	(Na ₂ SeO ₃)	NT	—	Noda et al. 1979
<i>B. subtilis</i> rec assay	(Na ₂ SeO ₄)	NT	+	Kanematsu et
	(SeO ₂)	NT	+	al. 1980
<i>B. subtilis</i> transformation	(SeO ₂)	NT	+	Nakamuro et
	(Na ₂ SeO ₃)	NT	+	al. 1976
	(Na ₂ SeO ₄)	NT	—	
Eukaryotic organisms:				
Mammalian cells	Chromosomal aberrations			
Chinese hamster ovary	(Na ₂ SeO ₃)	NT	+	Whiting et al.
	(Na ₂ SeO ₄)	NT	+	1980
Human leukocytes	(SeO ₂)	NT	+	Nakamuro et
	(Na ₂ SeO ₃)	NT	+	al. 1976
	(Na ₂ SeO ₄)	NT	—	
Human lymphocytes	(Na ₂ SeO ₄)	NT	+	Biswas 1997
Human lymphocytes	(Na ₂ SeO ₃)	NT	+	Biswas et al.
	(Na ₂ SeO ₄)	NT	+	2000
Human lymphocytes	(Na ₂ SeO ₃)	NT	+	Khalil 1989
	(Selenomethionine)	NT	+	
Cultured human fibroblasts	(Na ₂ SeO ₃)	+	+	Lo et al. 1978
	(Na ₂ SeO ₄)	—	—	
	Tetraploidy			
Chinese hamster V79 cells	(Na ₂ SeO ₃)	NT	+	Ueda et al.
	(Trimethylselenonium)	NT	+	1997
	DNA strand breaks			

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Table 3-4. Genotoxicity of Selenium *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Mouse mammary carcinoma cells	(Na ₂ SeO ₃)	NT	+	Lu et al. 1995b
	(Na ₂ SeO ₄)	NT	+	
	(Methylselenocyanate)	NT	–	
	(Se-methylseleno-cysteine)	NT	–	
	Unscheduled DNA synthesis			
Cultured human fibroblasts	(Na ₂ Se)	NT	+	Whiting et al. 1980
	(Na ₂ SeO ₃)	NT	+	
	(Na ₂ SeO ₄)	NT	+	
	Sister chromatid exchange			
Cultured human fibroblasts	(Na ₂ SeO ₃)	NT	+	Ray et al. 1978
Human lymphocytes	(Na ₂ SeO ₃)	NT	+	Khalil 1989
	(Selenomethionine)	NT	+	
	(Selenocystine)	NT	+	Khalil 1994

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NT = not tested; (Na₂Se) = sodium selenide; (Na₂SeO₃) = sodium selenite; (Na₂SeO₄) = sodium selenate; (SeO₂) = selenium dioxide

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Table 3-5. Genotoxicity of Selenium *In Vivo*

Species (test system)	End point	Results	Reference
Human lymphocytes (Na ₂ SeO ₃)	Chromosomal aberrations, sister chromatic exchanges	–	Norppa et al. 1980a
Monkey (<i>Macaca fasciculari</i>) bone marrow (L-seleno- methionine)	Micronuclei	+ (adult toxic dose) – (fetal at maternally toxic doses)	Choy et al. 1989 Choy et al. 1993
Mouse bone marrow (Na ₂ SeO ₃) (Na ₂ SeO ₄)	Chromosome breaks and spindle disturbances	+ +	Biswas et al. 1997
Mouse bone marrow (Na ₂ SeO ₃) (Na ₂ SeO ₄)	Chromosome breaks and spindle disturbances	+ +	Biswas et al. 1999a
Mouse bone marrow (H ₂ SeO ₃) (Na ₂ SeO ₄)	Micronucleus induction	+ +	Itoh and Shimada 1996
Mouse bone marrow (H ₂ SeO ₃)	Micronucleus induction	+	Rusov et al. 1996
Rat bone marrow (Na ₂ SeO ₃)	Chromosomal aberrations	+	Newton and Lilly 1986
Rat bone marrow (SeS)	Chromosomal aberrations	–	Moore et al. 1996b
Rat bone marrow (SeS)	Micronucleus induction	+	Moore et al. 1996b
Rat spleen (SeS)	Chromosomal aberrations	–	Moore et al. 1996b
Rat spleen (SeS)	Micronucleus induction	–	Moore et al. 1996b
Rat lymphocytes (Na ₂ SeO ₃)	Chromosomal aberrations	–	Newton and Lilly 1986

+ = positive result; – = negative result

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The addition of glutathione to test mixtures enhances the genotoxicity of sodium selenite, sodium selenate, and sodium selenide in bacterial test systems, indicating that production of a reactive species mutagenic for bacteria occurs via a reductive mechanism following concomitant exposure to these compounds (Whiting et al. 1980). This finding is supported by results in mammalian test systems. For example, in cultured human leukocytes, sodium selenite induces chromosome aberrations and sister chromatid exchanges (Nakamuro et al. 1976; Ray and Altenburg 1978; Ray et al. 1978). Sister chromatid exchange was not observed at similar sodium selenite concentrations in a human lymphoblastoid cell line; however, exchanges were observed when these same cells were incubated with sodium selenite and red blood cell lysate (Ray and Altenburg 1978). The observation that internal constituents of red blood cells may contribute to the genotoxicity of sodium selenite supports the suggestion that metabolism is involved in the production of an active species following exposure to sodium selenite in these test systems. The active species responsible for the genotoxic effects is not known.

At high concentrations, sodium selenite induces unscheduled DNA synthesis and chromosome aberrations in cultured human fibroblasts (Lo et al. 1978). The addition of a metabolic activator (S9 fraction) or glutathione increased both the number of aberrations and the toxicity of sodium selenite (Whiting et al. 1980) and sodium selenate (Lo et al. 1978; Whiting et al. 1980).

Sodium selenite, sodium selenide, methylselenocyanate, and Se-methylselenocysteine were all found to be cytotoxic to cells of a mouse mammary carcinoma line; however, only sodium selenite and sodium selenide induced DNA strand breaks (Lu et al. 1995b).

Selenomethionine (Khalil 1989) and selenocystine (Khalil 1994) have tested positive for sister chromatid exchanges in cultured human lymphocytes. Selenomethionine, sodium selenite, and sodium selenate tested positive for chromosomal aberrations in cultured human lymphocytes (Biswas 1997; Biswas et al. 2000; Khalil 1989). Sodium selenite was considerably more clastogenic than sodium selenate (Biswas et al. 2000).

The genotoxicity of selenium monosulfide was assessed in an *in vivo/in vitro* micronucleus and chromosome aberration assay in rats (Moore et al. 1996b). Male Wistar rats (4/dose) were administered 25, 50, or 100 mg/kg selenium monosulfide in corn oil. Negative control rats received corn oil by gavage and positive controls were injected intraperitoneally with 20 mg/kg cyclophosphamide. Animals were sacrificed 24 hours after treatment and the femur marrow and spleen were removed and cultured. Spleen

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and marrow cultures were examined 24 or 48 hours after establishment, respectively. No increase in chromosome aberrations or micronucleus formation in cells from treated rats was observed.

Results of *in vivo* genotoxicity tests have been both negative and positive (Table 3-5). Chromosomal aberrations and sister chromatid exchanges in lymphocytes were not increased in nine neuronal ceroid lipofuscinosis patients treated with intramuscular sodium selenite injections or tablets (0.005–0.05 mg selenium/kg/day) for 1–13.5 months, or in five healthy persons given selenite (0.025 mg/kg/day) for 2 weeks (Norppa et al. 1980a). Among the treated patients, there was no distinction between route of exposure.

Compared to untreated controls, a significant increase in the number of micronuclei was observed in bone marrow cells of macaques treated by nasogastric intubation with L-selenomethionine at a dose of 0.24 mg selenium/kg/day for 15 days (Choy et al. 1989). No effect on the number of micronuclei was observed in macaques treated with L-selenomethionine at a dose of 0.12 mg selenium/kg/day for 19 days. A significant increase in the number of micronuclei in bone marrow cells was not observed in the offspring of macaques treated by nasogastric intubation with L-selenomethionine at a dose of 0.12 mg selenium/kg/day on gestation days 20–50 (Choy et al. 1993). The doses of L-selenomethionine used in these studies produced obvious signs of toxicity (loss of body weight, poor appetite, constipation, depression, weakness) in the macaques.

Chromosomal aberrations were not increased in the lymphocytes of rats given two intravenous doses of sodium selenite at 2.3–2.7 mg selenium/kg (Newton and Lilly 1986). Chromosomal aberrations in bone marrow cells were significantly increased in these rats, but the total dose of selenium was near the intravenous LD₅₀ for selenite, which has been reported as 5.7 mg selenium/kg in rats (Olson 1986).

Bone marrow cells of male mice gavaged with sodium selenate or sodium selenite showed a significant increase in chromosome breaks and spindle disturbances compared with untreated controls (Biswas et al. 1997, 1999a). The number of chromosomal aberrations increased with dose and was slightly greater with sodium selenite than with sodium selenate. A significant increase in micronucleus formation was observed in bone marrow cells of male mice intraperitoneally injected with selenous acid and in female mice intramuscularly injected with sodium selenite, but not in male mice intraperitoneally injected with sodium selenate (Itoh and Shimada 1996; Rusov et al. 1996).

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Selenium appears to affect the ability of liver enzymes to activate some chemical mutagens. Studies in animals exposed orally to sodium selenite in the diet at doses between 0.05 and 0.125 mg selenium/kg/day indicate that selenium may inhibit the mutagenic effect of other chemical agents (Gairola and Chow 1982; Schillaci et al. 1982). In these studies, *S. typhimurium* was used to assess the mutagenicity of DMBA, benzo[a]pyrene (BAP), and 2-aminoanthracene (2AA) in the presence of liver microsomal enzymes from rats fed either a basal diet (0.02–0.15 mg selenium/kg diet or 0.001–0.0075 mg selenium/kg/day) or a sodium selenate-supplemented diet (basal diet plus 1–5 mg selenium/kg/diet or 0.05–0.25 mg selenium/kg/day) for 3–20 weeks. DMBA and 2AA were found to be less mutagenic in the presence of liver microsomal enzymes taken from rats fed the selenium-supplemented diets than in the presence of microsomal enzymes taken from rats fed the basal diet; BAP mutagenicity was not changed.

The genotoxicity of selenium monosulfide was assessed in *in vivo* micronucleus and chromosome aberration assays in rats (Moore et al. 1996b). Male Wistar rats (5/dose/timepoint) were administered 12.5, 25, or 50 mg/kg selenium monosulfide in corn oil. Negative control rats received corn oil by gavage and positive controls were injected intraperitoneally with 20 mg/kg cyclophosphamide. Animals were sacrificed 24, 36, or 48 hours after treatment and the femur marrow and spleen cells were examined. A small, but significant increase in micronucleated bone marrow cells was observed 24 hours after treatment with 50 mg/kg selenium monosulfide and 48 hours after treatment with 12.5 mg/kg selenium monosulfide. Selenium monosulfide was cytotoxic at the 50 mg/kg dose after 24 hours. No increase in micronucleus formation was observed in the spleen. No increase in chromosome aberrations was observed in the bone marrow or spleen.

3.4 TOXICOKINETICS

Occupational studies indicate that humans absorb elemental selenium dusts and other selenium compounds, but quantitative inhalation toxicokinetic studies in humans have not been done. Studies in dogs and rats indicate that following inhalation exposure, the rate and extent of absorption vary with the chemical form of selenium. Studies in humans and experimental animals indicate that, when ingested, several selenium compounds including selenite, selenate, and selenomethionine are readily absorbed, often to greater than 80% of the administered dose. Although a study of humans did not detect evidence of dermal absorption of selenomethionine, one study of mice indicates selenomethionine can be absorbed dermally. There is little or no information available on the absorption of selenium sulfides, but selenium disulfides are not believed to be absorbed through intact skin.

Selenium accumulates in many organ systems in the body; in general, the highest concentrations are found in the liver and kidney (Table 3-6). Selenium concentrations in tissues do not seem to be correlated with effects. Tissue concentrations were highest in pigs fed D,L-selenomethionine, while a similar dose of selenium (form not stated) given as *A. bisulcatus* was a more potent neurotoxin. Blood, hair, and nails also contain selenium, and selenium has been found in human milk (Table 3-7). In addition, selenium is subject to placental transfer.

As a component of glutathione peroxidase and the iodothyronine 5'-deiodinases, selenium is an essential micronutrient for humans. Its role in the deiodinase enzymes may be one reason that growing children require more selenium than adults. Selenium is also a component of the enzyme thioredoxin reductase, which catalyses the NADPH-dependent reduction of the redox protein thioredoxin. Other selenium-containing proteins of unknown functions, including selenoprotein P found in the plasma, have also been identified. Excess selenium administered as selenite and selenate can be metabolized to methylated compounds and excreted.

Selenium is primarily eliminated in the urine and feces in both humans and laboratory animals. The distribution of selenium between the two routes seems to vary with the level of exposure and time after exposure. The form of selenium excreted is dependent on the form of selenium that was ingested. In cases of acute exposure to toxic concentrations of selenium or selenium compounds, significant amounts of selenium can be eliminated in the breath, causing the characteristic "garlic breath."

A number of metabolism and other toxicokinetic studies of selenium are nutritional studies designed to answer a nutritional question, not a toxicological question. For example, the dose used may not be toxic, but may be meant to provide information on how a dose relevant to selenium deficiency or cancer chemoprevention might be handled in the body. Since the metabolism of selenium is a function of the dose ingested, these studies may be of limited toxicological relevance.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Studies regarding the absorption of selenium in humans following inhalation exposure are limited to occupational studies. Glover (1970) examined urinary selenium levels of workers employed in a

Table 3-6. Selenium Concentrations in Human Tissues^{a,b}

Selenium concentration			Country	Reference
Mean	SD	Range		
Fetal tissues				
Liver (µg selenium/g)				
2.8	0.2		United States	Robkin et al. 1973 ^c
Blood (mg selenium/L)				
0.12	0.008		United States	Hadjimarkos et al. 1959
1.04	0.28		United States	Baglan et al. 1974 ^c
0.070	0.017		New Zealand	Thompson and Robinson 1980
0.061	0.014		Scandinavia	Korpela et al. 1984
Erythrocytes (mg selenium/L)				
0.39	0.08		United States	Rudolph and Wong 1978
0.149			Scandinavia	Haga and Lunde 1978
0.104	0.026		New Zealand	Thompson and Robinson 1980
Plasma (mg selenium/L)				
0.13	0.03		United States	Rudolph and Wong 1978
0.033	0.008		New Zealand	Thompson and Robinson 1980
Serum (mg selenium/L)				
0.052			Scandanavia	Haga and Lunde 1978
Adult/Infant tissues				
Adrenal gland (µg selenium/g)				
0.46	0.03		United States	Blotcky et al. 1979
0.21 (infant)			Canada	Dickson and Tomlinson 1967
0.36 (adult)				
Brain (µg selenium/g)				
	0.021	0.114–0.171	Denmark	Larsen et al. 1979
0.11			Germany	Oster et al. 1988c
0.16 (infant)			Canada	Dickson and Tomlinson 1967
0.27 (adult)				
		0.115–0.222	Japan	Ejima et al. 1996
Fat (µg selenium/g)				
0.09 (infant)			Canada	Dickson and Tomlinson 1967
0.12 (adult)				
Gonad (µg selenium/g)				
0.46 (infant)			Canada	Dickson and Tomlinson 1967
0.47 (adult)				

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Table 3-6. Selenium Concentrations in Human Tissues^{a,b}

Selenium concentration			Country	Reference
Mean	SD	Range		
Heart (µg selenium/g)				
0.33	0.13		United States	Blotcky et al. 1979
0.170	0.032		Germany	Oster et al. 1988c
0.155	0.030 (LV)			
0.55 (infant)			Canada	Dickson and Tomlinson 1967
0.22 (adult)				
Intestine (µg selenium/g)				
0.31 (infant)			Canada	Dickson and Tomlinson 1967
0.22 (adult)				
Kidney (µg selenium/g)				
0.89	0.11		United State	Blotcky et al. 1979
0.771	0.169		Germany	Oster et al. 1988c
0.92 (infant)			Canada	Dickson and Tomlinson 1967
0.63 (adult)				
0.78	0.19	0.36–1.29	Sweden	Muramatsu and Parr 1988
Liver (µg selenium/g)				
0.62	0.04		United States	Blotcky et al. 1979
0.50	0.08	0.35–0.65	United States	Zeisler et al. 1984
1.73	0.24		United States	McConnell et al. 1975 ^c
		0.27–0.51	Denmark	Larsen et al. 1979
0.291	0.078		Germany	Oster et al. 1988c
0.995	0.308		Finland	Alfthan et al. 1991 ^c
0.45	0.11		Finland	Aaseth et al. 1990
0.06			Bulgaria	Damyanova 1983
0.33	0.12	0.082–0.64	Sweden	Muramatsu and Parr 1988
0.19	0.05	0.10–0.27	New Zealand	Casey et al. 1983
0.34 (infant)			Canada	Dickson and Tomlinson 1967
0.39 (adult)				
Lung (µg selenium/g)				
0.30	0.02		United States	Blotcky et al. 1979
0.132	0.033		Germany	Oster et al. 1988c
0.17 (infant)			Canada	Dickson and Tomlinson 1967
0.21 (adult)				
Pancreas (µg selenium/g)				
0.55	0.13		United States	Blotcky et al. 1979
0.63	0.07		United States	McConnell et al. 1975 ^c
0.05 (infant)			Canada	Dickson and Tomlinson 1967
0.13 (adult)				

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Table 3-6. Selenium Concentrations in Human Tissues^{a,b}

Selenium concentration			Country	Reference
Mean	SD	Range		
Prostate (µg selenium/g)				
0.26	0.02		United States	Blotcky et al. 1979
0.150	0.035		Germany	Oster et al. 1988c
Skeletal muscle (µg selenium/g)				
0.40	0.20		United States	Blotcky et al. 1979
0.111	0.017		Germany	Oster et al. 1988c
0.31 (infant)			Canada	Dickson and Tomlinson 1967
0.40 (adult)				
		0.13–0.21	Denmark	Larsen et al. 1979
Skin (µg selenium/g)				
0.24	0.02		United States	Blotcky et al. 1979
Spleen (µg selenium/g)				
0.37	0.03		United States	Blotcky et al. 1979
0.226	0.044		Germany	Oster et al. 1988c
0.37 (infant)			Canada	Dickson and Tomlinson 1967
0.27 (adult)				
Stomach (µg selenium/g)				
0.19 (infant)			Canada	Dickson and Tomlinson 1967
0.17 (adult)				
Testis (µg selenium/g)				
0.28	0.03		United States	Blotcky et al. 1979
0.274	0.048		Germany	Oster et al. 1988c
Thyroid (µg selenium/g)				
1.02	0.20		United States	Blotcky et al. 1979
0.72	0.44	0.15–1.90	Finland	Aaseth et al. 1990
0.64 (infant)			Canada	Dickson and Tomlinson 1967
1.24 (adult)				

^aGeneral population measures unless otherwise noted^bSelenium concentrations in adult blood and blood components, urine, hair, nails, milk, placenta, and semen are found in Table 3-7.^cDry weight

LV = left ventricle; RV = right ventricle; SD = standard deviation

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Table 3-7. Biomarkers: Selenium Concentrations in Human Tissues and Fluids^a

Selenium concentration				
Mean	SD	Range	Country	Reference
Whole blood (mg selenium/L)				
0.132	0.029	0.08–0.13	United States	Corden et al. 1989
0.206		0.10–0.30	United States	Allaway et al. 1968
0.109	0.015		United States	Dworkin et al. 1986
0.157		0.103–0.191	United States	Shamberger 1983
0.182	0.037		Canada	Dickson and Tomlinson 1967
0.095	0.009		China	Zhu 1981
0.095	0.091		China	Yang et al. 1983
0.164	0.032		Greece	Bratakos et al. 1990
0.108	0.006	0.076–0.140	Italy	Minoia et al. 1990
		0.079–0.103	Finland	Jaakkola et al. 1983
		0.080–0.089	Finland	Kumpusalo et al. 1990 ^b
		0.077–0.089	Finland	Kumpusalo et al. 1990 ^c
0.069	0.018		New Zealand	Thomson and Robinson 1980 ^d
0.059	0.012		New Zealand	Rea et al. 1979
0.092	0.001	0.06–0.013	Germany	Oster et al. 1988b
Erythrocyte (mg selenium/L)				
0.174		0.11–0.28	United States	Meyer and Verreault 1987
0.13	0.02		United States	Dworkin et al. 1986
0.52	0.05		United States	Rudolph and Wong 1978 ^d
0.131	0.002	0.060–0.210	Germany	Oster et al. 1988b
		0.057–0.087	New Zealand	Watkinson 1981
0.074	0.016		New Zealand	Rea et al. 1979
0.103	0.030		New Zealand	Thomson and Robinson 1980
Plasma (mg selenium/L)				
0.155		0.081–0.225	United States	Clark et al. 1984
0.095	0.016		United States	Dworkin et al. 1986
0.21	0.03		United States	Rudolph and Wong 1978 ^d
0.148			United States	Coates et al. 1988
0.081	0.016		Canada	Dickson and Tomlinson 1967
0.153	0.021		Japan	Hojo 1987
0.089	0.014		Netherlands	van't Veer et al. 1990
0.081	0.001	0.056–0.105	Italy	Minoia et al. 1990
0.118	0.027	0.064–0.173	Italy	Sesana et al. 1992
0.048	0.010		New Zealand	Rea et al. 1979
0.041	0.011		New Zealand	Thomson and Robinson 1980 ^d

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Table 3-7. Biomarkers: Selenium Concentrations in Human Tissues and Fluids^a

Selenium concentration				
Mean	SD	Range	Country	Reference
Serum (mg selenium/L)				
0.136	0.002		United States	Willett et al. 1983
0.110	0.016		United States	Menkes et al. 1986
0.162	1.48		United States	Coates et al. 1988
0.07			United States	McConnell et al. 1975 ^e
0.125	0.047 ^g		United States	DHHS 1997
0.198	0.055	0.123–0.363	United States	Longnecker et al. 1991
0.143	0.016		Canada	Lalonde et al. 1982 ^f
0.081	0.001	0.033–0.121	Italy	Minoia et al. 1990
		0.087–0.093	Italy	Morisi et al. 1989
0.118	0.016	0.087–0.308	Finland	Luoma et al. 1992
0.055	0.001		Finland	Virtamo et al. 1987
0.073	0.015		South Africa	Heese et al. 1988 ^d
0.207		0.07–0.81	Venezuela	Brätter et al. 1991a
		0.229–0.621	Venezuela	Brätter and Negretti De Brätter 1996
Urine (mg selenium/L)				
0.034	0.024		England	Glover 1970
0.058	0.026	0.020–0.113	Japan	Hojo 1981a
0.026	0.012		China	Yang et al. 1983
0.024	0.002		Greece	Bratakos et al. 1990
0.022	0.002	0.002–0.031	Italy	Minoia et al. 1990
Hair (µg selenium/g)				
0.64	0.02		United States	Thimaya and Ganapathy 1982
0.359	0.004		China	Zhu 1981
0.36	0.17		China	Yang et al. 1983
0.42	0.88		Greece	Bratakos et al. 1990
0.42	0.10	0.21–0.63	Sweden	Muramatsu and Parr 1988 ^e
3.40	2.0	0.95–9.6 (female)	Japan	Imahori et al. 1979 ^e
3.70	2.3	0.06–14.2 (male)		
1.02	1.04	Maternal	England	Razagui and Haswell 1997
0.63	0.52	Neonatal		
0.54	0.34	Maternal	Spain	Bermejo Barrera et al. 2000
0.77	0.24	Child		
Nails (µg selenium/g)				
1.56	0.58	0.083–3.82	United States	Longnecker et al. 1991
0.82	0.174		United States	Hunter et al. 1990a
0.63	0.12		Netherlands	van't Veer et al. 1990
0.54	0.91		Greece	Bratakos et al. 1990
0.78		0.085–2.75	Netherlands	Van Noord et al. 1992

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Table 3-7. Biomarkers: Selenium Concentrations in Human Tissues and Fluids^a

Selenium concentration				
Mean	SD	Range	Country	Reference
Milk (µg selenium/mL)				
		0.208–0.256	Africa	Funk et al. 1990 ^b
0.018	0.004	0.007–0.033	United States	Shrearer and Hadjimarkos 1975
0.021		0.013–0.053	United States	Hadjimarkos 1963
0.016	0.005			Smith et al. 1990
0.026			United States	Ellis et al. 1990
0.062	0.055	0.015–0.214	Chile	Cortez 1984
0.010	0.002	0.006–0.013	Finland	Kumpulainen 1983
0.011			Austria	Li et al. 1999
0.012			Germany	Michalke and Schramel 1998
		0.025–0.250	Venezuela	Brätter et al. 1991a
		0.043–0.112	Venezuela	Brätter and Negretti De Brätter 1996
Placenta (mg selenium/L)				
1.70	0.61		United States	Baglan et al. 1974 ^e
0.193	0.016		United States	Korpela et al. 1984
0.18	0.007		United States	Hadjimarkos et al. 1959
Semen (µg selenium/g)				
0.063	0.020	0.016–0.131	Singapore	Roy et al. 1990
1.80	0.11		Finland	Suistomaa et al. 1987 ^e

^aGeneral population measures unless otherwise noted^bRange of mean concentration^cRange of mean concentrations for multivitamin users^dOnly women were sampled.^eDry weight^fOnly men were sampled.^gStandard error of the mean

SD = standard deviation

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selenium rectifier plant. Workers exposed to higher levels of unspecified inorganic selenium compounds in the air excreted higher levels of selenium in their urine than workers in other areas of the plant with lower concentrations of selenium in the air. Although the study indicates that selenium was absorbed from the lungs of the workers, the nonspecific exposure levels and lack of compound identification precluded an estimate of the extent and rate of absorption from the lungs. Significantly increased serum selenium levels were reported for workers at a rubber tire repair shop in Toluca City, Mexico compared with a group of unexposed individuals from the same city (Sánchez-Ocampo et al. 1996). The workers in this study were exposed to selenium (no levels reported) from vulcanized rubber, both as dust in the air and from handling the tires; thus, it is not possible to attribute absorption to a single route.

Studies using dogs and rats indicate that absorption of selenium following inhalation exposure is extensive, although the rate of absorption depends on the chemical form of selenium. In rats (Medinsky et al. 1981a) and dogs (Weissman et al. 1983), the absorption of selenium following inhalation exposure to selenious acid aerosol is approximately twice as rapid as the absorption of selenium following inhalation exposure to elemental selenium aerosol. However, Medinsky et al. (1981a) found that with either form after 4 days most of the selenium was absorbed following inhalation exposure and that the distribution of selenium in the body tissues was identical, suggesting that selenium entered the same body pool following pulmonary uptake (Medinsky et al. 1981a).

3.4.1.2 Oral Exposure

Selenium compounds are generally readily absorbed from the human gastrointestinal tract. The bioavailability of ingested selenium can be affected by the physical state of the compound (e.g., solid or solution), the chemical form of selenium (e.g., organic, inorganic), and the dosing regimen. However, in general, it appears that the degree of selenium absorption (i.e., percent of administered dose absorbed) in humans is independent of the exposure level, but that in some cases, absorption is greater when selenium deficiency exists.

In humans, absorption of sodium selenite or selenomethionine can exceed 80% for both small and relatively large doses (Griffiths et al. 1976; Thomson 1974; Thomson and Stewart 1974; Thomson et al. 1977). A total of 90–95% of a small amount of sodium selenite (0.010 mg selenium/person) administered in aqueous solution was absorbed (Thomson 1974). Absorption of a large dose (1.0 mg/person) of either

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sodium selenite or selenomethionine was 90–95 and 97% of the administered dose, respectively (Thomson et al. 1977). These data indicate a lack of homeostatic control over the dose range tested. Martin et al. (1989a) found no clear evidence of increased gastrointestinal absorption of selenium as sodium selenite in aqueous solution by healthy male volunteers kept on a selenium-deficient diet. Griffiths et al. (1976) reported 96–97% absorption of a single dose of 0.002 mg selenium administered as selenomethionine in solution. Similarly, Thomson et al. (1977) reported 97% absorption of a single large dose of 1.0 mg selenium administered as selenomethionine in solution to one subject. The subjects in these studies were New Zealand women.

Other studies have indicated that humans might absorb selenomethionine more efficiently than sodium selenite (Moser-Veillon et al. 1992; Swanson et al. 1991). Young et al. (1982) studied human absorption of dietary selenium in young men in the United States. The men ate either ⁷⁵Se-labeled chicken alone (0.013 mg selenium/person) or the chicken plus supplemental labeled sodium selenite (0.071 mg selenium/person in a solution mixed with the meal). Eighty percent of the selenium in the chicken meat was absorbed, but less than 30% of the selenium administered as sodium selenite was absorbed. Similarly, Robinson et al. (1978) found that 75% of selenomethionine, but only 46% of selenite, was absorbed during a 10–11-week administration of solutions providing 0.0013–0.0023 mg selenium/kg/day to New Zealand women. It is not clear why the estimated absorption of sodium selenite varied between 46 and 30% in these trials.

Experimental animals also efficiently absorb selenium compounds from the gut independent of the level of selenium exposure. Several studies have reported absorption of 80–100% in rats given dietary selenium administered as sodium selenite, sodium selenate, selenomethionine, or selenocystine (Furchner et al. 1975; Thomson and Stewart 1973). Other animal species also readily absorb orally administered selenium compounds. Furchner et al. (1975) estimated that over 90% of an oral dose of selenious acid was absorbed in mice and dogs, although monkeys absorbed less of the administered dose (amount unspecified). Using an *in vivo* perfusion method in which selenite was added directly to the duodenal end of the small intestine, the absorption of selenite was linearly related to concentration (slope=0.0386) in the range of 1–200 μ M (Chen et al. 1993).

In one study of rats, absorption of selenite or selenomethionine into the blood stream following oral exposure occurred primarily in the duodenum and, to a lesser extent, in the jejunum and ileum (Whanger et al. 1976). Compared to the small intestine, little selenium was absorbed from the stomach (Whanger et al. 1976), and it was not determined whether absorption occurred in the large intestine. In an *in vitro*

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study using everted intestinal sacs from hamsters, Spencer and Blau (1962) found that selenomethionine was transported against a concentration gradient with the same characteristics as methionine.

Selenomethionine was not found to be degraded during transport. This study suggests that in the intestines, methionine and selenomethionine share the same transport mechanism.

A comparison of absorption of selenium by selenium-depleted rats after oral administration of sodium selenate, selenomethionine, or methyl selenocysteine (from high-selenium broccoli) found that gross absorption of selenium from methyl selenocysteine was significantly lower (85%) than from sodium selenate or selenomethionine (91%); further, true selenium absorption adjusted for urinary excretion was significantly different for methyl selenocysteine, sodium selenate, and selenomethionine, with the lowest absorption for methyl selenocysteine and the highest for selenomethionine (Finley 1998). Absorption of selenium from selenomethionine was not significantly lower than from sodium selenate.

In vivo experiments with ligated rat intestines have shown that there is significantly higher absorption and transfer to the body of selenium as selenocystine or selenodiglutathione than selenium as selenite from ligated loops of ileum, but that absorption of the three forms of selenium in the jejunum was approximately similar (Vendeland et al. 1992). *In vitro* experiments with brush border membrane vesicles derived from rat intestines have shown dramatic differences in the uptake and binding of selenium depending on the form in which it is presented, with absorption of organic forms being much more efficient than absorption from selenite or selenate (Vendeland et al. 1992, 1994). Selenium from selenocystine or selenodiglutathione was absorbed 10 times more quickly than selenium from sodium selenite (Vendeland et al. 1992). Similarly, selenium was much more efficiently absorbed from selenomethionine than from selenite or selenate (Vendeland et al. 1994). Binding also varied between selenomethionine, selenite, and selenate, with selenite binding exceeding that of selenate by 37-fold and selenomethionine exceeding selenite by 14-fold (Vendeland et al. 1994). These studies indicate that absorption of selenium from the gastrointestinal tract of animals is pH-dependent and influenced by the presence of sulfhydryl-containing compounds, and that the increased absorption of selenium with sulfhydryl compounds is likely due to complex formation with these compounds.

3.4.1.3 Dermal Exposure

Dermal absorption was tested in eight women at a maximum dose of 0.0029 mg selenium/kg as selenomethionine (0.05% L-selenomethionine in a lotion). No detectable increase in serum selenium concentrations was observed, but because the concentrations tested were so low, absorption cannot be

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ruled out (Burke et al. 1992a). Absorption of selenium disulfide was examined using a monthly 24-hour urine specimen in 16 persons who washed their hair weekly with a 1% selenium disulfide shampoo. No differences were found from control urinary selenium levels over the 1-year exposure period (Cummins and Kimura 1971). No absorption of selenium from selenium sulfide was seen in 15 persons who applied a 2.5% selenium sulfide suspension to their torsos and allowed it to remain on the body overnight (Kalivas 1993).

Mice were treated with a maximum of 0.02% selenium as selenomethionine by topical application of a lotion 3 times per week for 39 weeks to the shaved back and ears (size of area not specified). The applied dose was 0.29 mg/kg/day. Controls received the lotion without selenium. Dermal effects were not observed in the selenomethionine-treated mice. However, treated animals had significantly higher concentrations of selenium than the controls in the liver and ventral skin away from the application site (Burke et al. 1992b). These data suggest that mice can absorb topically applied selenomethionine, but since the areas were not occluded, some oral absorption during grooming is also possible.

3.4.2 Distribution

Most studies report similar distribution patterns for both organic and inorganic selenium compounds tested. In plasma, selenium mainly distributes into three plasma proteins, namely selenoprotein P, glutathione peroxidase, and albumin (Ducros et al. 2000). Approximately 3% of total plasma selenium is bound to lipoproteins, mainly to the LDL fraction, and the selenium may be incorporated as selenomethionine in place of methionine during protein synthesis and/or bound to cysteine residues by selenium-sulfur bonds. Selenoprotein P is an extracellular protein in the plasma. It is suggested that selenoprotein P is involved in the transport of selenium and as an antioxidant, but its biochemical function has not yet been established (Burk and Hill 2000; Hill and Burk 1989; Yang et al. 1989b).

Normal levels of selenium found in various human tissues are shown in Table 3-6. Selenium concentrations in human fluids and tissues that are easily collected (e.g., placenta) are provided in Section 3.8.1, Biomarkers Used to Identify or Quantify Exposure to Selenium. Selenium from sodium selenite and sodium selenate is found at the highest concentrations in the liver and kidney of humans and other animals following oral administration or intravenous or subcutaneous injection (Cavalieri et al. 1966; Heinrich and Kelsey 1955; Jereb et al. 1975; Thomson and Stewart 1973). Similarly, monkeys receiving high doses of L-selenomethionine orally for up to 30 days accumulated the highest

concentrations of selenium in the liver and kidneys (Willhite et al. 1992). Selenium from selenomethionine tends to be retained in tissues at higher concentrations (3–10-fold greater) and for longer periods of time than inorganic selenium compounds. The increased selenium tissue concentrations are not due to the slightly greater absorbance of selenomethionine (Butler et al. 1990; Grønbaek and Thorlacius-Ussing 1992; Ip and Hayes 1989; Salbe and Levander 1990b), but rather to the slower elimination as a consequence of its incorporation into body proteins (Stadtman 1983, 1987, 1990).

3.4.2.1 Inhalation Exposure

No studies were located regarding the distribution of selenium in humans after inhalation of elemental selenium or selenium compounds.

Weissman et al. (1983) reported that selenium concentrated in the liver, kidney, spleen, and lungs of dogs following inhalation exposure to selenious acid or elemental selenium aerosols.

3.4.2.2 Oral Exposure

A study of 100 paired samples of maternal and neonate hair found that the concentration in neonatal hair (0.63 ± 0.52 µg/g) was lower than in maternal hair (1.02 ± 1.04 µg/g), but the results were not analyzed statistically (Razagui and Haswell 1997). Levels of selenium in 30 paired samples of the hair of a mother and her child found no correlation between the selenium concentration of the hair of the mother and her child (Bermejo Barrera et al. 2000). The average level of selenium in the children's hair (0.77 ± 0.24 µg/g) was higher than that of their mothers (0.54 ± 0.34 µg/g). The higher concentration of selenium in the children's hair could represent increased absorption or retention, but no information was provided in the study as to the age of the children or to possible differences in dietary intake of selenium between mother and child.

A study in rats found that young (weanling) animals accumulated more selenium in their tissues than adults (Salbe and Levander 1989). Selenium-deficient rats were fed diets supplemented with the same amounts of selenium, as sodium selenate or L-selenomethionine, for 4 weeks. Hair and nail selenium levels in adults were 10–20% and ~50% lower, respectively, than the amounts found in weanlings. Skeletal muscle and red blood cell selenium levels were ~50 and ~35% lower, respectively, in adults than weanlings, whereas levels in the liver were generally similar between the two growth phases.

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Selenomethionine caused greater deposition of selenium in the tissues than sodium selenate in both adults and weanlings, although the percent increase was similar for the two compounds in both growth phases. In rats and dogs, the selenium arising from sodium selenite administered in drinking water or in the diet is widely distributed in the body, although concentrated primarily in the liver and kidney (Furchner et al. 1975; Sohn et al. 1991; Thomson and Stewart 1973).

In most studies, selenium from selenomethionine accumulates in tissues to a greater extent than equal administered doses of selenium from selenite or selenate. Behne et al. (1991) reported higher liver and muscle selenium concentrations in rats receiving selenium orally as selenomethionine for 3 or 6 weeks than as selenite for the same length of time. Ip and Hayes (1989) reported similar results for blood, liver, kidney, and skeletal muscle. Salbe and Levander (1990b) compared distribution of dietary selenomethionine and selenate in rats and found higher selenium concentrations in plasma, erythrocytes, liver, muscle, hair, and nails in animals receiving selenomethionine. (Hair and nails have been used to gauge long-term human selenium exposure and were, therefore, included in this study.) Monkeys receiving selenomethionine in drinking water for 11 months had selenium concentrations in plasma, erythrocytes, liver, muscle, and hair that were 3–10-fold greater than monkeys receiving selenite (Butler et al. 1990). The higher levels of selenium found after selenomethionine compared to selenite treatment are likely a result of a greater retention of selenium from selenomethionine, rather than a difference in absorption. Butler et al. (1990) indicate that dietary ascorbic acid can reduce selenite absorption, but not selenomethionine absorption. Therefore, the differential effect of ascorbic acid on selenium absorption may have contributed to the difference in selenium content of tissues observed in monkeys treated with selenite, compared to monkeys treated with selenomethionine. Studies of rats indicate that the central nervous system also concentrates more selenium when administered as selenomethionine than when administered as inorganic selenium compounds (Grønbaek and Thorlacius-Ussing 1989, 1992; Zi-Jian Jie 1992).

A comparison of distribution of selenium in selenium-depleted rats after oral administration of sodium selenite, sodium selenate, selenomethionine, or methyl selenocysteine (from high-selenium broccoli) revealed that the rate of restoration of selenium in the liver and muscle was significantly slower for methyl selenocysteine than other forms of selenium (Finley 1998). The rate of repletion in muscle was significantly faster for selenomethionine than other groups, but kidney and plasma showed no significant difference in the rate of repletion for any form of selenium. The rate of repletion of glutathione peroxidase activity in the tissues was similar to the rate of repletion of the tissue itself and was slowest when methyl selenocysteine was the administered form.

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Another study of distribution of selenium in selenium-deficient rats fed either sodium selenite or selenomethionine found that the concentration of selenium in blood and hair increased with administered dose, but was higher for selenium administered as selenomethionine (Shiobara et al. 1998).

A study of dietary supplementation of female pigs with 0.1 or 0.3 ppm selenium from a selenium-enriched yeast or from sodium selenite (doses not given) from 60 days before breeding until weaning found that the concentration of selenium in milk, dam, and offspring tissues increased with the dose of selenium administered and was higher when the source of selenium was the selenium-enriched yeast (Mahan and Kim 1996).

A study using pigs indicates that tissue levels of selenium do not correlate with effects. Tissue concentrations of selenium were higher in pigs fed 1.25 mg selenium/kg/day as D,L-selenomethionine than in pigs fed the same dose of selenium as *A. bisulcatus* or selenate, although neurological effects were more severe and occurred after fewer days of treatment with *A. bisulcatus* (Panter et al. 1996). The form of selenium in *A. bisulcatus* is unknown, although Panter et al. (1996) indicate that it is nonprotein.

In poultry, selenium is concentrated in the pancreas to a greater extent following oral administration of selenomethionine than following oral administration of sodium selenite (Cantor et al. 1975). The differential ability of the two compounds to concentrate in the pancreas of birds may explain why selenium administered as selenomethionine is more effective than the same dose of selenium administered as sodium selenite in preventing pancreatic fibrosis in chicks, a condition indicative of selenium deficiency (Cantor et al. 1975).

The distribution profiles of single oral or intravenous doses of selenium (2 mg selenium/kg as sodium selenite) administered to Wistar rats were dependent on the route of administration (Kaneko et al. 1999). Selenium concentration was highest in the kidney or liver, followed by the heart, lung, or spleen; then plasma and the brain. Oral administration produced lower doses of selenium than injection in all organs except the kidney where levels produced by the two routes were comparable (this may reflect the importance of urine as a route of excretion).

Following oral exposure, selenium is found in human milk (Brätter and Negretti De Brätter 1996; Brätter et al. 1991b; Li et al. 1999; Michalke and Schramel 1998; Moser-Veillon et al. 1992; Rodríguez Rodríguez et al. 1999; Viitak et al. 1995; Yang 1989b). Selenium is also found in the milk of mice, rats,

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dogs, pigs, cows, and monkeys (Abdelrahman and Kincaid 1995; Archimbaud et al. 1992; Bañuelos and Mayland 2000; Chhabra and Rao 1994; Hawkes et al. 1994; Mahan and Kim 1996; Parizek et al. 1971a). This supplies offspring with selenium during the time period in which they are fed exclusively on milk (about 6 months for humans). Transplacental transfer of selenium has been demonstrated in humans, rats, hamsters, dogs, pigs, and monkeys (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Jandial et al. 1976; Mahan and Kim 1996; Parizek et al. 1971a; Willhite et al. 1990).

3.4.2.3 Dermal Exposure

Although unable to detect increased selenium in human females exposed to selenomethionine dermally, Burke and coworkers found elevated liver and skin selenium concentrations in mice treated with a topical lotion containing selenomethionine applied to the shaved back and ears (size of area not specified), although since the areas were not occluded, some oral absorption during grooming is also possible (Burke et al. 1992a, 1992b). In rats, between 9 and 27% of dermally applied selenious acid was absorbed, as measured in ⁷⁵Se radioisotope studies (Medinsky et al. 1981b).

3.4.2.4 Other Routes of Exposure

In humans, selenium has been found to be widely distributed to organs and tissues following injection of sodium selenite, sodium selenate, and selenomethionine, with the highest concentrations generally found in the liver and kidneys (Ben-Porath and Kaplan 1969; Cavalieri et al. 1966; Jereb et al. 1975; Lathrop et al. 1972). In studies involving injection of radiolabelled selenium, the pancreas accumulated high concentrations of radiolabelled selenium immediately following injection, but within hours, the selenium rapidly disappeared from this organ (Lathrop et al. 1972). Using an *in vitro*, dually perfused, human term placenta, selenite has also been shown to cross the human placenta (Eisenmann and Miller 1994). Further, following intravenous injection, ⁷⁵Se from selenomethionine was found to cross the near-term human placenta (Jandial et al. 1976).

There is a rapid decline in serum selenium levels 1 hour after intravenous administration of sodium selenite or sodium selenate to humans (Burk 1974; Nelp and Blumberg 1965). Burk (1974) found that 50% of the plasma selenium was protein-bound within the first 2 hours after administration; 85% was bound within 4–6 hours after administration; and 95% was bound after 24 hours. Circulating alpha-2 globulins have been reported to have the greatest affinity for selenium (Hirooka and Galambos 1966a).

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Burk (1974) found that lipoproteins, primarily the very low density lipoprotein (VLDL) and the low-density lipoprotein (LDL) fractions, were also involved in selenium binding.

In vitro studies of human plasma and whole blood incubated with sodium selenite have indicated that selenite is accumulated in erythrocytes by an active transport mechanism (Lee et al. 1969). Several studies indicate that the selenite is chemically altered in the erythrocyte and then transported back into the plasma, where the selenium metabolite binds to plasma proteins (Burk 1974; Hirooka and Galambos 1966a; Lee et al. 1969).

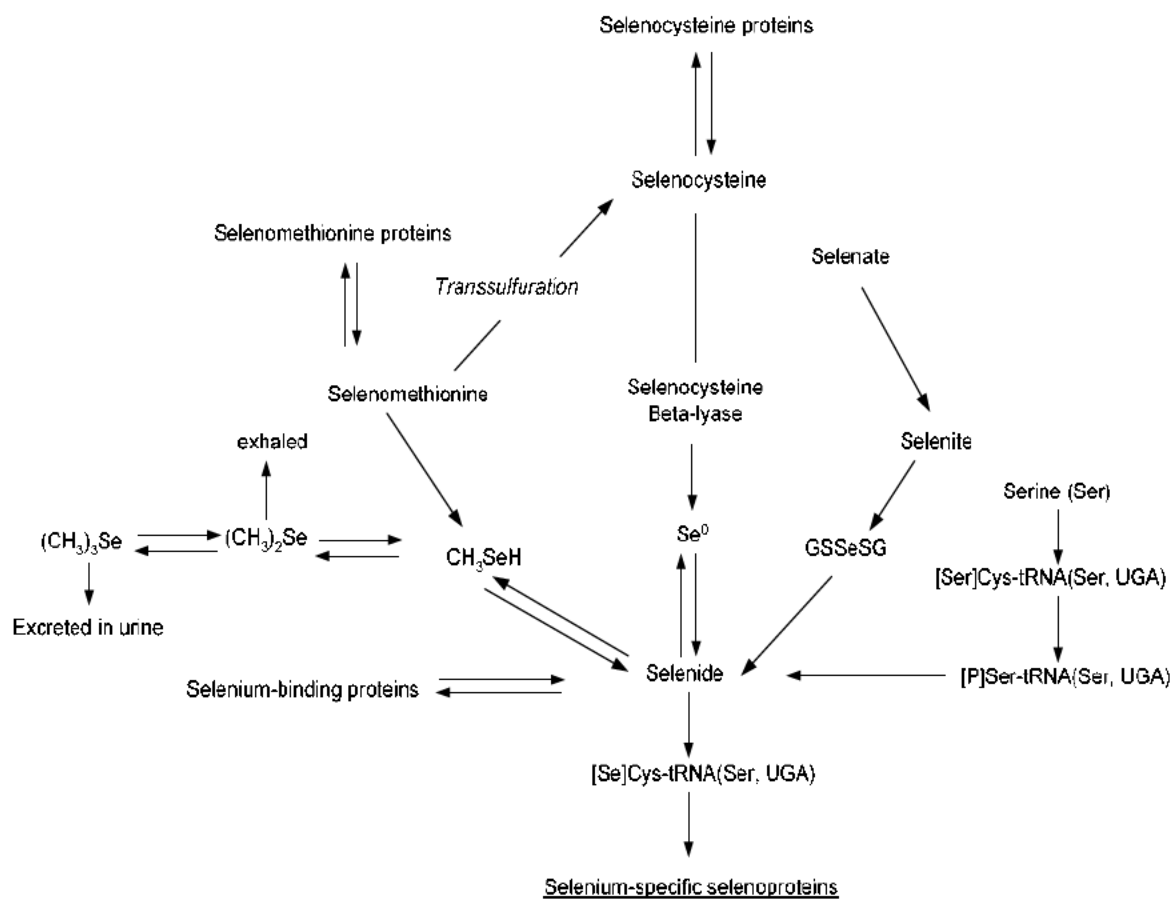
A high degree of protein binding of selenium in the plasma has also been demonstrated in experimental animals. Sandholm (1973) found that selenite administered intravenously to mice can be metabolically altered by erythrocytes to a form that binds to plasma proteins. In mice, rats, and dogs, selenite initially binds to albumin. Later, selenite can be found bound to alpha and gamma globulins in rats and to alpha-2 and beta-1 globulins in dogs (Imbach and Sternberg 1967; Sternberg and Imbach 1967).

3.4.3 Metabolism

The metabolic fate of selenium, an essential element, is outlined in Figure 3-4. In summary, inorganic selenium is reduced stepwise to the assumed key intermediate hydrogen selenide, and it (or a closely related species) is either incorporated into selenoproteins after being transformed to selenophosphate and selenocysteinyl tRNA according to the UGA codon encoding selenocysteinyl residue, or excreted into urine after being transformed into methylated metabolites of selenide (Lobinski et al. 2000).

Consequently, selenium is mainly present in the mammalian body in forms of covalent carbon-selenium bonds, particularly selenoprotein P (the principal selenoprotein in plasma), selenoenzymes such as glutathione peroxidases (enzymes that catalyze the reduction of peroxidases and thereby protect cells from oxidative damage), type 1-iodothyronine deiodinase (which catalyzes the deiodination of thyroxine to triiodothyronine), and thioredoxin reductase (which may trigger cell signaling in response to oxidative stress) (Holmgren and Kumar 1989; Lobinski et al. 2000). Additional information regarding the metabolism of selenium is discussed below.

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Figure 3-4. Metabolic Pathways for Selenium*

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Four classes of selenoproteins have been defined (Sunde 1990): selenium-specific proteins, proteins incorporating selenocysteine at cysteine codons, proteins incorporating selenomethionine at methionine position in those proteins, and proteins that bind selenide nonspecifically. The selenium-specific proteins, which include the enzymes glutathione peroxidase, thyroxine reductase, and iodothyronine 5'-deiodinase, constitute the most physiologically important class of selenoproteins. These proteins contain selenocysteine that is incorporated cotranslationally using selenide and serine as the precursors. This process is specified by a uracil-guanine-adenine (UGA) codon, which usually functions as a stop codon. A stem-loop structure in the 3' untranslated region is required for UGA to specify selenocysteine (Berry et al. 1991). This cotranslational process is the only known pathway for the production of selenocysteine in humans. In contrast to selenocysteine, selenomethionine cannot be biosynthesized by human tissues (Levander 1986).

The second and third classes of selenoproteins form in a similar manner: selenomethionine bound to the transfer ribonucleic acid (tRNA) for methionine competes with methionine bound to the tRNA for methionine at methionine codons, and selenocysteine bound to the tRNA for cysteine competes with cysteine bound to the tRNA for cysteine at cysteine codons (Sunde 1990). The amount of selenoamino acids incorporated into protein is dependent on the ratio of the selenoamino acid and the amino acid bound to the amino acid tRNA.

The last class of selenoproteins contains the selenium binding proteins. This is an operational class defined by Sunde (1990) as "selenoproteins with selenium bound tightly enough so that the selenium remains attached during standard protein purification procedures that produce discrete selenium labeled species." This class contains selenoproteins that have not been fully characterized.

As indicated in Figure 3-4, selenide, which can nonspecifically bind to proteins, is a central selenium species in the pathways leading to the formation and degradation of selenium proteins. Selenide is also formed from selenite by reduction via glutathione following uptake in red blood cells. This reaction occurs in rat (Gasiewicz and Smith 1978) and human (Lee et al. 1969) red blood cells, as well as in human plasma containing added glutathione (Mas and Sarker 1989). Selenide is then transported to the plasma, bound selectively to albumin and transferred to the liver, and methylated for excretion in the urine, or incorporated into proteins after being transformed into selenium-phosphate and selenocysteinyl

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tRNA according to the UGA codon encoding selenocysteinyl residue (Ganther and Lawrence 1997). Unlike selenite, selenate appears to be either taken up directly by the liver or excreted in urine by rats (Suzuki and Ogra 2002).

Selenocysteine can also be metabolized to selenide. This reaction requires a specific enzyme, selenocysteine β -lyase, which catalyzes the decomposition of selenocysteine to alanine and hydrogen selenide. The enzyme requires pyridoxal 5-phosphate as a cofactor. In humans, the highest levels of selenocysteine β -lyase activity are found in the liver, followed by the kidney, heart, adrenal gland, and muscle (Daher and Van Lente 1992). In mice orally exposed to selenocysteine, an intermediate metabolite selenocysteine-glutathione selenyl sulfide is formed in the small intestine and transported to the liver via the blood plasma (Hasegawa et al. 1995, 1996b). This compound can be nonenzymatically reduced by excess glutathione or enzymatically reduced by glutathione reductase in liver cytosol extracts to reform selenocysteine, which can be further metabolized.

When not immediately metabolized, selenomethionine can be incorporated into tissues such as skeletal muscle, liver, pancreas, stomach, gastrointestinal mucosa, and erythrocytes (Schrauzer 2000). Selenomethionine metabolism to selenide and the incorporation into selenium-specific proteins may occur by two pathways: metabolism to methane selenol and selenide or via selenocysteine. Evidence that the incorporation of selenium from selenomethionine into protein is by the transsulfuration pathway (methionine to cysteine) comes from studies of selenomethionine metabolism in lymphoblast cell lines deficient in cystathionine lyase and cystathionine synthetase, enzymes of the transsulfuration pathway (Beilstein and Whanger 1992). Deficiency in these enzymes greatly reduces the incorporation of selenomethionine into glutathione peroxidase.

Similar to metals, elemental selenium, a non-metal, is transformed into methylated metabolites prior to being excreted into the urine and/or exhaled. Methylation is a detoxification pathway for selenium, and the extent of methylation is dose-dependent (Kobayashi et al. 2002). Monomethylated selenium is excreted as the major form in urine at deficient, normal, and low-toxic levels of selenium. When monomethylated selenium reaches a plateau in the urine (i.e., in the toxic dose range of selenium), trimethylated selenium in the urine and dimethylated selenium in the expired air increase. The major monomethylated form of selenium has been thought to be methyselenol, but Kobayashi et al. (2002) identified it as a selenosugar (1 β -methylselenol-*N*-acetyl-D-galactosamine).

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Humans accidentally exposed to high levels of selenium have been reported to have a noticeable garlic odor of the breath, probably as a result of excretion of dimethyl selenide in expired air (Bopp et al. 1982; Wilbur 1980). Garlic odor of the breath has been noted in humans following ingestion of toxic levels of sodium selenate (Civil and McDonald 1978) and following inhalation of elemental selenium dust or selenium dioxide (Glover 1970).

In human populations with sufficient levels of selenium, dietary selenium is apparently partitioned into a selenite-exchangeable storage pool and a selenite-nonexchangeable storage pool. The selenite-exchangeable pool shows saturation kinetics. After this pool is filled, dietary selenium as selenomethionine may be the primary determinant of selenium bioavailability and serum selenium concentrations (Meltzer et al. 1990, 1992). There is experimental support for the concept that selenium metabolism can be divided into non-specific and specific components (Burk et al. 2001). Selenomethionine is the non-specific component as it appears to be incorporated into plasma proteins, presumably as selenomethionine, in proportion to its presence in the methionine pool. There is no indication that selenocysteine and inorganic selenium (selenate) were incorporated non-specifically into plasma protein, suggesting that these forms are metabolized by specific selenium metabolic processes. For example, selenocysteine seems to incorporate selenium into selenoproteins, but not into other proteins in place of cysteine (Burk et al. 2001). Selenate was either taken up directly by the liver or excreted in the urine, and selenite was taken up by red blood cells, reduced to selenide by glutathione, and then transported to the plasma and transferred to the liver (Suzuki and Ogra 2002). Data from both humans and Rhesus monkeys indicate that the selenium concentration in glutathione peroxidase is independent of the form of selenium administered and suggest a metabolic saturation at average intake rates (Butler et al. 1990; Meltzer et al. 1990).

In macaques that were orally administered doses of 0.025–0.3 mg selenium/kg as L-selenomethionine for up to 30 days, both erythrocyte selenium and glutathione peroxidase-specific activity showed a delay before increasing in a dose-related manner (Hawkes et al. 1992). At 0.15 and 0.3 mg selenium/kg, glutathione peroxidase-specific activity in erythrocytes continued to increase for 15 days after cessation of treatment and remained elevated through the end of the study (40 days after the end of treatment). The investigators attributed this effect to an initial deposition of selenium into a nonspecific pool (such as substitution for methionine in serum proteins), followed by slow release into the erythrocyte. Wistar rats also show incorporation of selenomethionine into proteins (Behne et al. 1991).

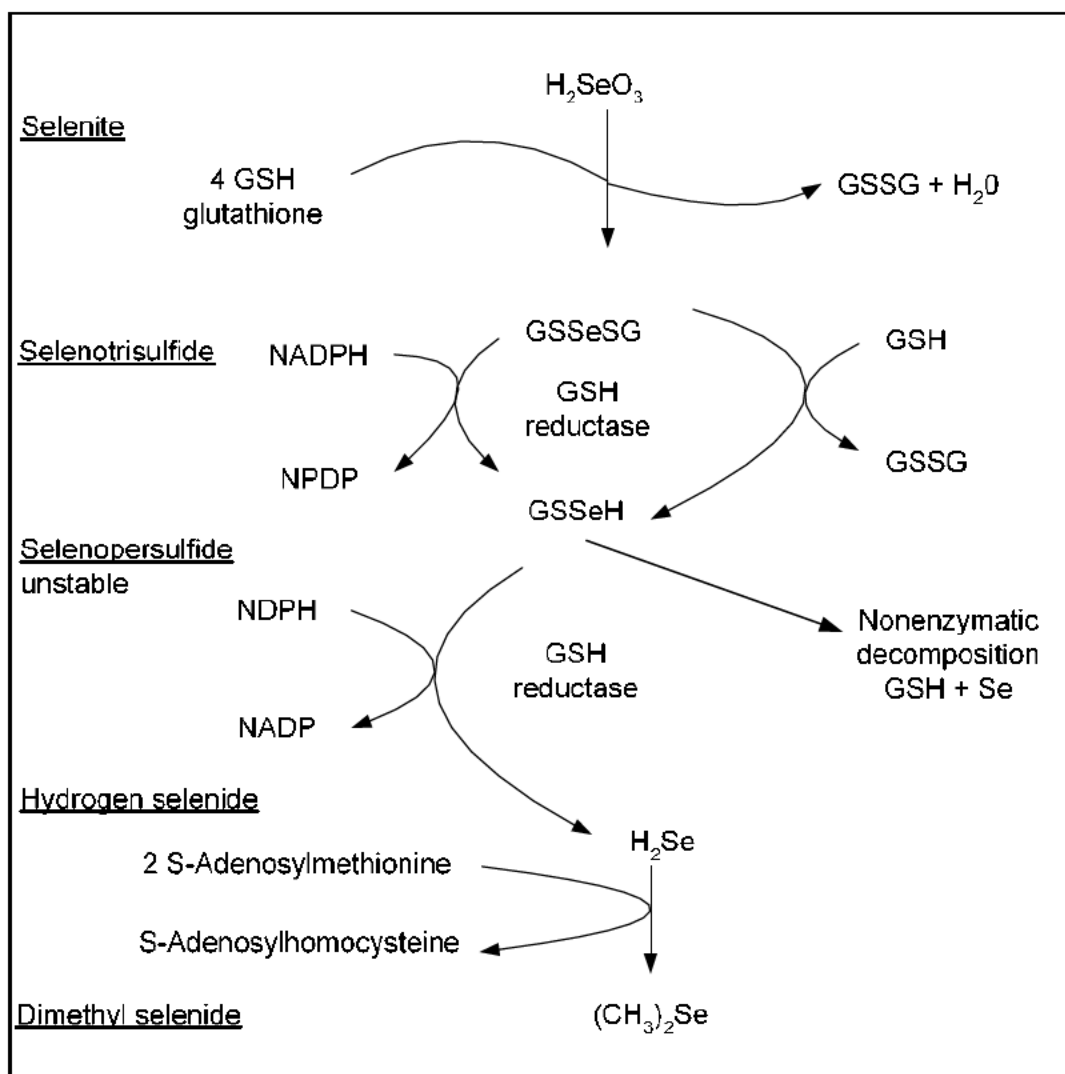
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In rats, dimethyl selenide has been identified as the primary respiratory metabolite following injection of sodium selenite or sodium selenate (Hirooka and Galambos 1966b) and appears to be produced in the liver (Nakamuro et al. 1977). In mice, dimethyl selenide and dimethyldiselenide have been detected in expired air following the addition of unspecified amounts of sodium selenite, D,L-selenomethionine, or D,L-selenocystine to their drinking water (Jiang et al. 1983). A third unidentified volatile selenium compound was detected in expired air of the mice following D,L-selenomethionine injection (Jiang et al. 1983).

In rats, the trimethylselenonium ion has been identified as the predominant urinary metabolite following intraperitoneal administration of sodium selenite (Byard and Baumann 1967), sodium selenate, selenomethionine, selenocystine, or methylselenocysteine, or following ingestion of seleniferous wheat (Palmer et al. 1970). A total of 30.8% of the urinary selenium was in the form of trimethylselenonium after administration of 15 ppm selenium in wheat. Another major selenium metabolite that appeared in the urine more slowly than the trimethylselenonium ion was identified chromatographically, but the chemical structure of that metabolite was not defined (Palmer et al. 1970).

Similarly, the trimethylselenonium ion was the major urinary metabolite of selenium excreted by rats after intraperitoneal injection of either methylselenocysteine (4 mg/kg) or selenocysteine (3 mg/kg) (Palmer et al. 1970). The amounts of trimethylselenonium ion excreted were 50.6 and 49.7% of the total urinary metabolites after methylselenocysteine and selenocysteine administration, respectively. In both cases, urinary metabolism accounted for only 10–15% of the administered dose. As selenium was not measured in feces or expired air, recovery of the dose was incomplete. In a review of the metabolic pathways resulting in the production of dimethyl selenide from selenite in rodents, Ganther (1979) indicated that reduction of selenite or selenate to dimethyl selenide requires glutathione and the methylating agent *S*-adenosylmethionine. NADPH, coenzyme A, ATP, and magnesium (II) salts are also required to provide optimal conditions for this reaction (Ganther 1979). Ganther (1971) and Hsieh and Ganther (1975) found that selenite initially reacts nonenzymatically with glutathione to form a selenotrisulfide derivative. The selenotrisulfide is then reduced nonenzymatically in the presence of glutathione or enzymatically by glutathione reductase in the presence of NADPH to a selenopersulfide (GSSeH). The selenopersulfide is unstable and decomposes to glutathione and selenium or is enzymatically reduced by glutathione reductase in the presence of NADPH to hydrogen selenide (Ganther 1971; Hsieh and Ganther 1975). Hydrogen selenide can be methylated by *S*-adenosylmethionine in the presence of selenium methyltransferase to form dimethyl selenide (Figure 3-5).

Figure 3-5. Proposed Pathway for Formation of Dimethyl Selenide from Selenite in Animals*



*Adapted from Hsieh and Ganther 1975 and Ganther 1971

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Selenate apparently is not converted to dimethyl selenide as readily as is selenite. Studies of selenate metabolism are limited in mammals, but studies using bacteria indicate that selenate must be activated prior to conversion to selenite (Bopp et al. 1982). Dilworth and Bandurski (1977) demonstrated that in the presence of ATP, magnesium (II) salts, and ATP-sulfurylase, yeast could convert selenate to eventually yield selenite (Figure 3-6). Data regarding the metabolism of selenium sulfide after administration to humans or other animals were not located in the literature.

3.4.4 Elimination and Excretion

Excretion of selenium can occur in the urine, feces, and expired air (Griffiths et al. 1976; Hawkes et al. 1992, 1994; Lathrop et al. 1972; McConnell and Roth 1966; Thomson and Stewart 1974). Sweat is a minor pathway of selenium excretion in humans (Levander et al. 1987). Moreover, the initial rate of excretion appears to be dose dependent (Lathrop et al. 1972; McConnell and Roth 1966; Thomson and Stewart 1974). Some researchers have found that urinary excretion and fecal excretion of selenium are similar, with each route contributing approximately 50% of the total output (Stewart et al. 1978). However, the proportion excreted via each route seems dependent on several factors, including the level of exposure, the time since exposure, and the level of exercise. Lactating women and subjects depleted of selenium have decreased excretion of selenium in the urine and feces (Martin et al. 1989a, 1989b; Moser-Veillon et al. 1992). At high selenium exposure levels, excretion of selenium in expired air becomes more significant (McConnell and Roth 1966; Olson et al. 1963).

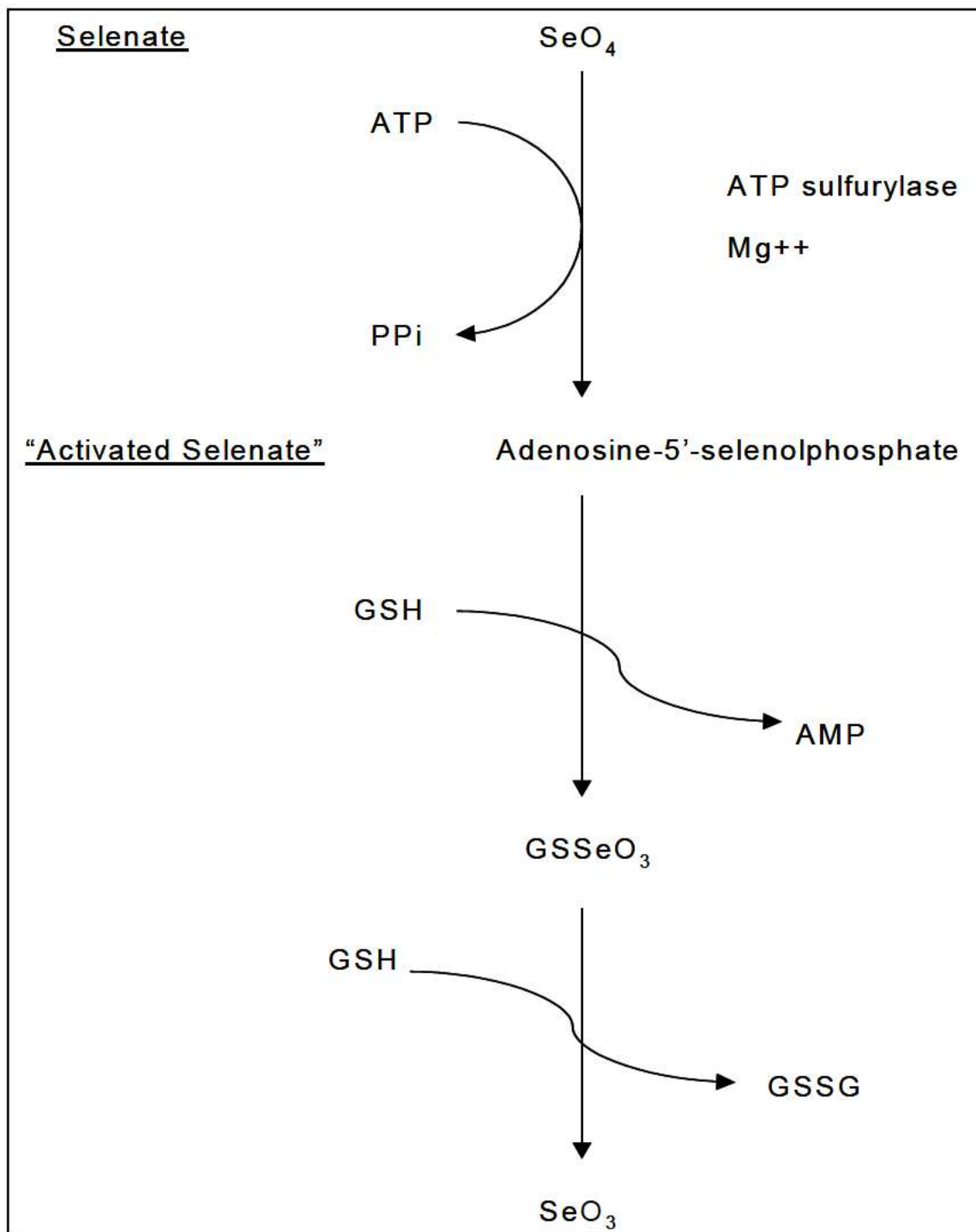
3.4.4.1 Inhalation Exposure

Following acute inhalation exposures to selenium compounds, humans excrete some of the absorbed dose in the expired air (Glover 1970), but no studies were located that actually quantified the rate of excretion or identified the selenium compounds in the expired air of humans.

3.4.4.2 Oral Exposure

Several human studies have indicated that the rate of urinary excretion is most rapid in the first 24 hours following oral administration or intravenous injection of sodium selenite (Kuikka and Nordman 1978;

Figure 3-6. Activation and Reduction of Selenate to Selenite in Yeast *Saccharomyces cerevisiae**



*Adapted from Dilworth and Bandurski 1977

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Thomson and Stewart 1974). Thomson and Stewart (1974) found that <6% of a trace dose (0.01 mg selenium) of orally administered sodium selenite was excreted in the urine within 24 hours of administration, whereas 64–73% of a 1-mg dose of selenium was excreted in the first 24 hours (Thomson 1974). Thomson et al. (1977) also found that a lower proportion of the selenium from an oral dose of 0.1 mg selenium administered as selenomethionine was excreted in the 24-hour urine than from a larger dose (1.0 mg selenium). Similarly, low selenium New Zealand residents excreted proportionally less selenium in their urine than North Americans of higher selenium status (Robinson et al. 1985), and there is limited evidence of such adaptation to selenium intake in some animal studies (Jaffe and Mondragon 1969, 1975; WHO 1987). Thus, when higher amounts of selenium are administered, a higher proportion of the selenium is excreted in the urine during the first 24 hours following exposure.

Decreasing urinary or fecal excretion appears to be the homeostatic mechanism by which the body retains greater amounts of selenium. Martin et al. (1989a) observed greater retention of selenium by individuals maintained on a selenium-deficient diet. This increase in retention was correlated with a decrease in fecal elimination. Similarly, the increased retention of selenium from selenomethionine compared to selenite was correlated with decreased elimination (Swanson et al. 1991). Lactating women have a greater retention of selenium from selenomethionine compared to selenite and a decreased urinary elimination (Moser-Veillon et al. 1992). Muscle activity seems to influence urinary excretion of selenium as demonstrated by the doubling of selenium concentration in the urine of women following vigorous exercise (Oster and Prellwitz 1990).

Less information is available regarding the elimination of selenium in the feces of humans than in the urine of humans. However, levels of fecal excretion of selenium have been reported to be similar to levels of urinary selenium excretion when dietary levels of selenium are not excessive (Patterson et al. 1989). Over a 14-day period, Stewart et al. (1978) found urinary elimination of selenium to average 0.013 mg selenium/day and fecal elimination of selenium to average 0.011 mg selenium/day in four New Zealand women exposed to 0.024 mg selenium/day in their normal diets. Balance data on 27 healthy U.S. adults (12 men and 15 women) similarly indicated an approximately even split between urine and fecal selenium excretion (Levander and Morris 1985). Determination of selenium balance at four time points (spring, summer, fall, and winter) showed respective average levels of selenium in the urine and feces of 48 ± 2 and 34 ± 1 $\mu\text{g/day}$ in the men, and 39 ± 1 and 23 ± 1 $\mu\text{g/day}$ in the women. Plasma selenium levels remained essentially constant during the year and were similar in the men and women, averaging 136 ± 4 and 133 ± 4 ng/L, respectively. Although the U.S. men consumed more selenium in the diet than the

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women, their selenium balance (8 ± 4) was less positive than the women (12 ± 3) because they tended to excrete more in the feces (Levander and Morris 1985). It has been suggested that some of the selenium content in feces can be attributed to biliary excretion (Levander and Baumann 1966a, 1966b).

In humans, whole body retention studies following oral administration of sodium selenite have indicated that selenium elimination is triphasic (Thomson and Stewart 1974). During the initial phase, which lasted about 1 week, elimination of selenium was rapid, with a half-life of approximately 1 day (Thomson and Stewart 1974). In the second phase, which also lasted approximately 1 week, selenium elimination was slower, with a half-life of 8–9 days. In the third phase, selenium elimination was much slower, with a half-life estimated to be 115–116 days. The first two elimination phases correspond to the fecal elimination of nonabsorbed selenium and the urinary excretion of absorbed but unutilized selenium (Thomson and Stewart 1974). Selenomethionine elimination is also triphasic; however, its terminal half-life is longer than that of sodium selenite. The average half-lives of selenomethionine for the three phases were measured to be approximately 0.4–2, 5–19, and 207–290 days, respectively (Griffiths et al. 1976). An examination of elimination data from 44 pigs exposed to excess selenium as sodium selenite in feed was found to fit a one-compartment model of selenium elimination (Davidson-York et al. 1999). Serum selenium levels were monitored over a period of 46 days beginning 1–14 days after termination of exposure to the feed containing excess selenium. Data were not adequate to depict the initial distribution phase, but a geometric mean elimination half-life of 12 days was calculated. It is likely that the period of elimination included in this study corresponds to the second phase described by Thomson and Stewart (1974).

The chemical form of selenium may play a role in determining how rapidly selenium is excreted in the urine. In rats, the rate of urinary excretion of selenium has been found to be greater following oral administration of sodium selenite than of selenomethionine (Thomson and Stewart 1973). A comparison of excretion of selenium by selenium-depleted rats after oral administration of sodium selenate, selenomethionine, or methyl selenocysteine (from high-selenium broccoli) found that excretion of selenium from methyl selenocysteine or selenomethionine was significantly lower than from sodium selenate; further, that there was no significant difference between secretion of selenium from methyl selenocysteine and selenomethionine (Finley 1998). This may contribute to the greater retention of selenium from selenomethionine, than from inorganic selenium (Martin et al. 1989a). However, another study of excretion of selenium from rats fed selenium as either sodium selenite or selenomethionine found that excretion of selenium increased with administered dose, but was similar for both forms of selenium (Shiobara et al. 1998).

As exposure to oral L-selenomethionine increased in macaques, the amount of selenium eliminated in the urine/day increased, as did the maximum rate of urinary excretion. However, the percentage of administered dose appearing in the urine decreased with an increase in dose (Hawkes et al. 1994).

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion of selenium by humans or other animals after dermal exposure to elemental selenium or selenium compounds.

3.4.4.4 Other Routes of Exposure

Whole body retention studies in sheep following injection of selenium have indicated that selenium excretion in animals follows a triexponential profile (Blodgett and Bevill 1987b; Ewan et al. 1967). In a 2-week study, Blincoe (1960) estimated the half-life for ⁷⁵Se in rats following intraperitoneal injection of ⁷⁵Se-labeled sodium selenite (0.93 mg selenium/kg). Initially, the excretion of selenium was rapid, with a half-life of approximately 0.8 day; the second phase of excretion was slower, with a half-life of 13 days. These results parallel the initial phases of selenium excretion seen in humans. The abbreviated duration of the Blincoe (1960) study did not permit the determination of a terminal elimination phase half-life. In rats, Ewan et al. (1967) found the final phase of elimination of selenium following a single subcutaneous injection of sodium selenite to be dose independent (from 0.008 mg selenium/kg to 2 mg selenium/kg), with a half-life of 65–78 days. Blodgett and Bevill (1987b) found the elimination rate of selenium in sheep during the second phase following a single intramuscular injection of sodium selenite to be dose dependent, with larger doses resulting in longer half-lives (i.e., doses of 0.4, 0.6, 0.7, or 0.8 mg selenium/kg resulting in half-lives for selenium elimination of 6.3, 8.8, 15.1, and 20.4 hours, respectively). The reasons for the decreasing elimination rate with increasing dose during the second phase are not clear.

Dietary levels of selenium and the individual's selenium nutritional status are the most important factors that influence the route and rate of selenium excretion. Selenium excretion in expired air is only significant when exposures to selenium are high. Rats injected subcutaneously with sodium selenite at doses of 2.2–5.4 mg selenium/kg excreted 41–62% of the administered selenium in exhaled air, whereas rats injected with sodium selenite at doses of 0.005–0.9 mg selenium/kg excreted only 0.2–11% of the

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administered selenium in expired air (McConnell and Roth 1966; Olson et al. 1963). As the amount of administered sodium selenite increased, the percent of the administered selenium excreted in the urine decreased (from approximately 22–33% of the administered selenium at doses of 0.005–0.9 mg selenium/kg to 3–14% of the administered selenium at doses of 3.1–5.4 mg selenium/kg) (McConnell and Roth 1966). Selenium in the feces was not measured in this study. Burk et al. (1972) found that as the dietary level of sodium selenite was increased, a larger proportion of an injected tracer dose of selenium (as sodium selenite) was excreted. At a dietary level of 0.005 mg selenium/kg, approximately 60% of the injected selenium had been excreted in the first 35 days following administration. At a dietary level of 0.05 mg selenium/kg, over 94% of the injected selenium had been excreted over the same period of time.

In experimental animals, other factors that can cause an increase in selenium levels in expired air are higher dietary levels of selenium, protein, or methionine (Ganter et al. 1966). Phenobarbital induction of microsomal enzymes has also led to increased exhalation of selenium following intravenous administration of sodium selenite (Sternberg et al. 1968).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of

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PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

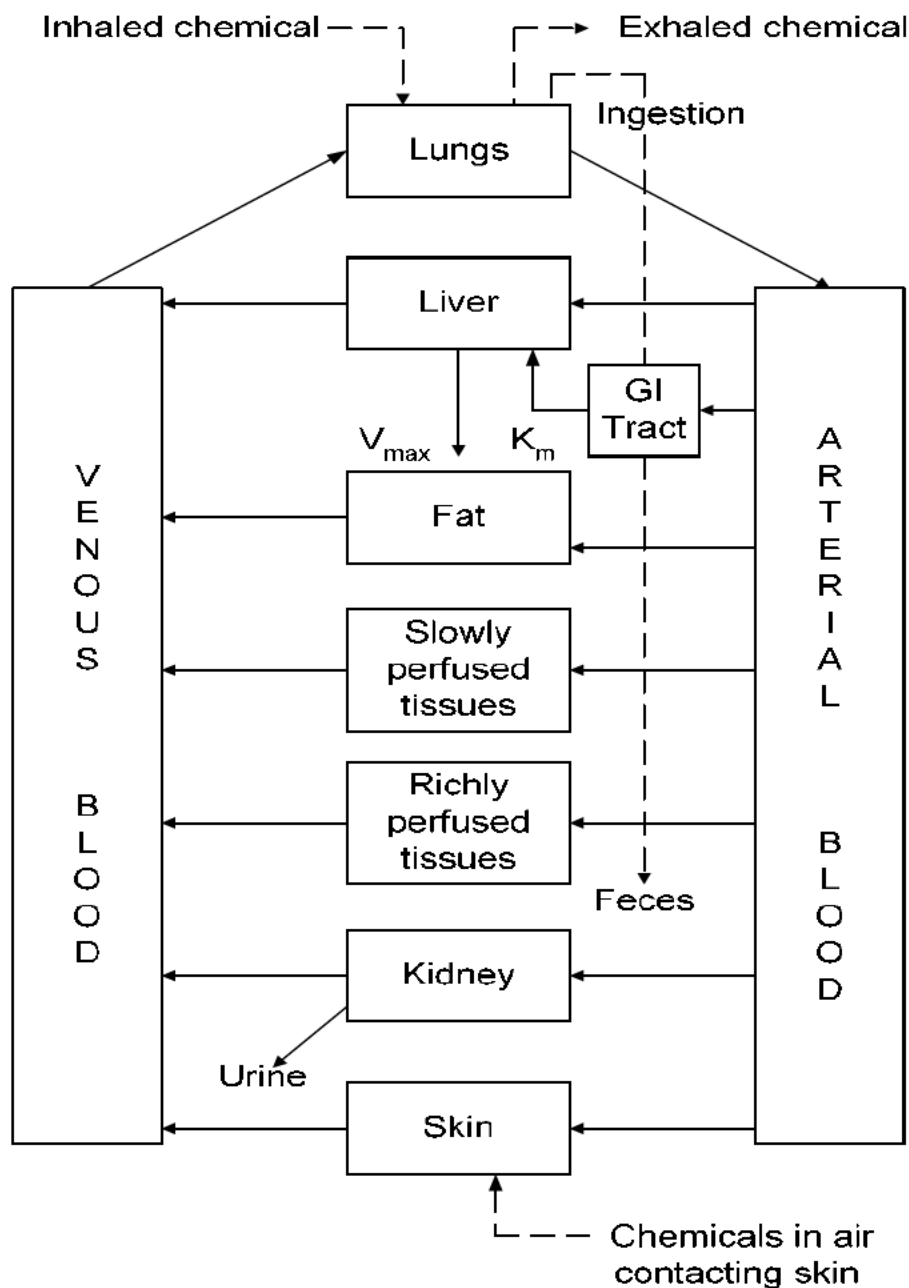
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-7 shows a conceptualized representation of a PBPK model.

Two models for selenium were located in the literature. Patterson and coworkers (Patterson and Zech 1992; Patterson et al. 1989, 1993) have developed compartmental models of the kinetics of selenium orally administered as selenite or selenomethionine in adult humans.

Figure 3-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

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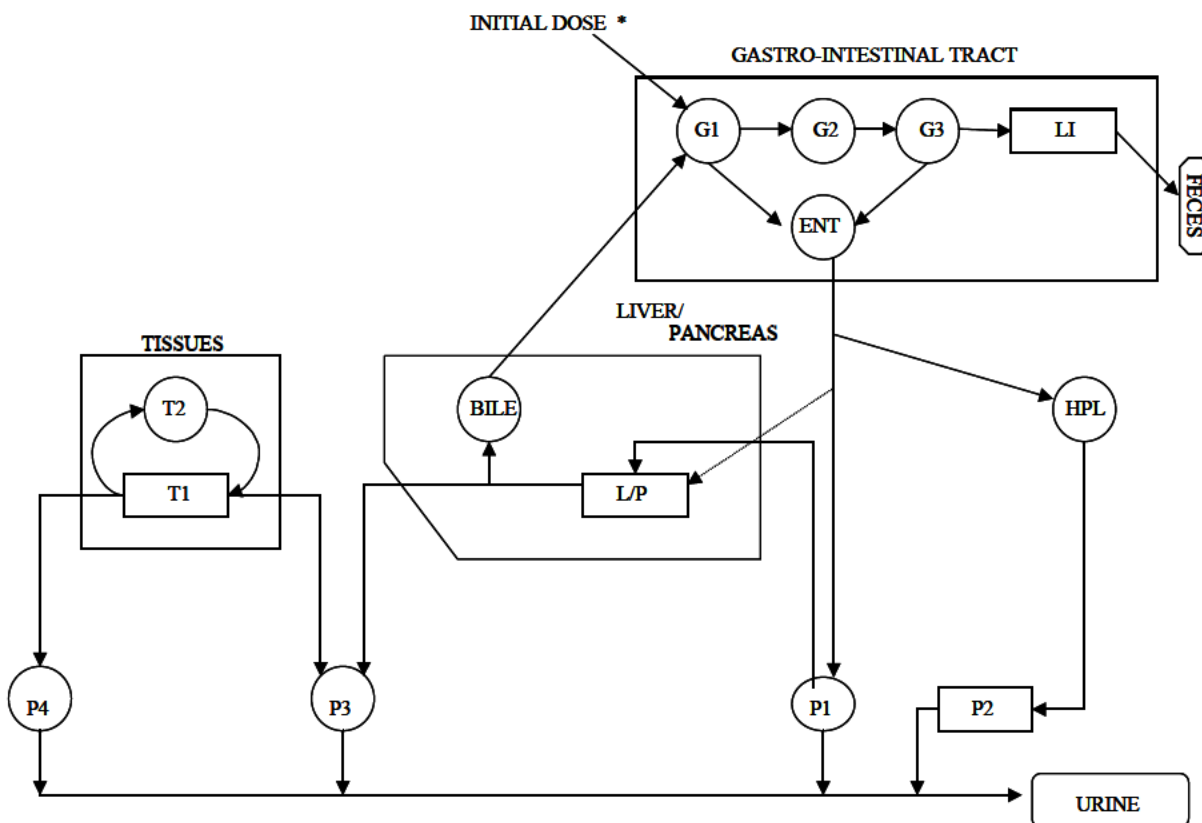
Patterson et al. (1989) Selenite Model

Description of the model. Patterson and coworkers (Patterson and Zech 1992; Patterson et al. 1989, 1993) developed a compartmental model of the kinetics of ingested selenite in adult humans based on data from human subjects who consumed a single oral dose of 200 μg ^{74}Se as selenite. The model assumes that 84% of the administered selenium is absorbed and that absorption is rapid. Absorbed selenite is assumed to distribute to six compartments: gastrointestinal tract, plasma, hepatopancreatic/lymphatic system, liver/pancreas, bile, and tissues (Figure 3-8). Unabsorbed selenium is excreted in the feces. Absorption occurs from the gastrointestinal compartment (probably the small intestine, but also possibly the stomach) into a rapidly turning-over pool (the intestinal cells or enterocytes) from which it leaves by two pathways. The central compartment is represented as four kinetically distinct plasma pools, P1 (the portal circulation), P2 (before passage through the liver), P3 (after passage through the liver), and P4 (after passage through the tissues). In the first pathway, selenium enters P1. The second pathway is to a liver/pancreatic compartment. Transport into and out of P1 is very rapid ($T_{1/2}$ approximately 0.36 hours) and this may represent selenium in the portal circulation passing through the liver before appearing in P3, but not removed in the first pass. The second pathway is via the hepatopancreatic/lymphatic system compartment to a second plasma pool (P2). Appearance of selenium in P2 is delayed ($T_{1/2}$ approximately 0.55 hours), representing the time needed to move through the hepatopancreatic/lymphatic system compartment. From the two plasma pools (P1 and P2), selenium can be excreted in the urine ($T_{1/2}$ approximately 3.94 and 1.96 hours, respectively) or it can move into the liver/pancreas compartment. After a delay of 4–6 hours, the selenium leaves the liver/pancreas either to a bile compartment ($T_{1/2}$ approximately 0.13 hours) and thence to the gut (G1) for excretion in feces or to a third plasma pool (P3) ($T_{1/2}$ approximately 0.19 hours). From P3, selenium can be excreted in the urine ($T_{1/2}$ approximately 4.15 hours) or can move into a large, slowly turning-over tissue compartment. Finally, selenium is transferred very slowly ($T_{1/2}$ approximately 1.27 hours) from the tissues (probably final metabolic products) to a fourth plasma pool (P4) and hence to the urine ($T_{1/2}$ approximately 6.54 hours).

Validation of the model. The extent to which this model has been validated is not described in Patterson and coworkers (Patterson and Zech 1992; Patterson et al. 1991, 1993).

Risk assessment. The model was designed to simulate the pharmacokinetics of selenium orally administered as selenite to humans as a preparation for a larger anticancer supplementation study jointly undertaken by the National Cancer Institute (NCI) and the U.S. Department of Agriculture (USDA) (Patterson and Zech 1992; Patterson et al. 1991, 1993).

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Figure 3-8. Selenite Model, a Kinetic Model for Selenite Metabolism

The arrow with an asterisk indicates the site of entry of the oral Se tracer. Arrows between compartments represent pathways of fractional transport. Compartments depicted as rectangles represent delays. Compartments G1, G2, G3, three-gut compartments, probably the small intestine; ENT, enterocytes (intestinal cells); HPL, compartment in hepato-pancreatic subsystem or lymphatic system; L/P, liver and pancreas; LI, large intestine; T1, T2, peripheral tissues, e.g., skeletal muscle, bone, kidney. Feces and urine compartments are drawn in the shape of test tubes to represent fractional (single) collections. The model includes absorption distributed along the gastrointestinal tract, enterohepatic recirculation, four-kinetically distinct plasma pools, P1–P4, a subsystem consisting of liver and pancreas, and a slowly turning-over tissue pool.

Source: Patterson et al. 1993

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Target tissues. The model is designed to simultaneously account for the appearance and disappearance of selenium in plasma, urine, and feces after administration of a single oral dose of ^{74}Se as selenite (Patterson and Zech 1992; Patterson et al. 1991, 1993).

Species extrapolation. The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interoute extrapolation. The model is designed to simulate oral exposures to selenite and cannot be applied to other routes of exposure without modification.

Extrapolation to other forms of selenium. The model is designed to simulate oral exposures to selenite and cannot be applied to other forms of selenium without modification.

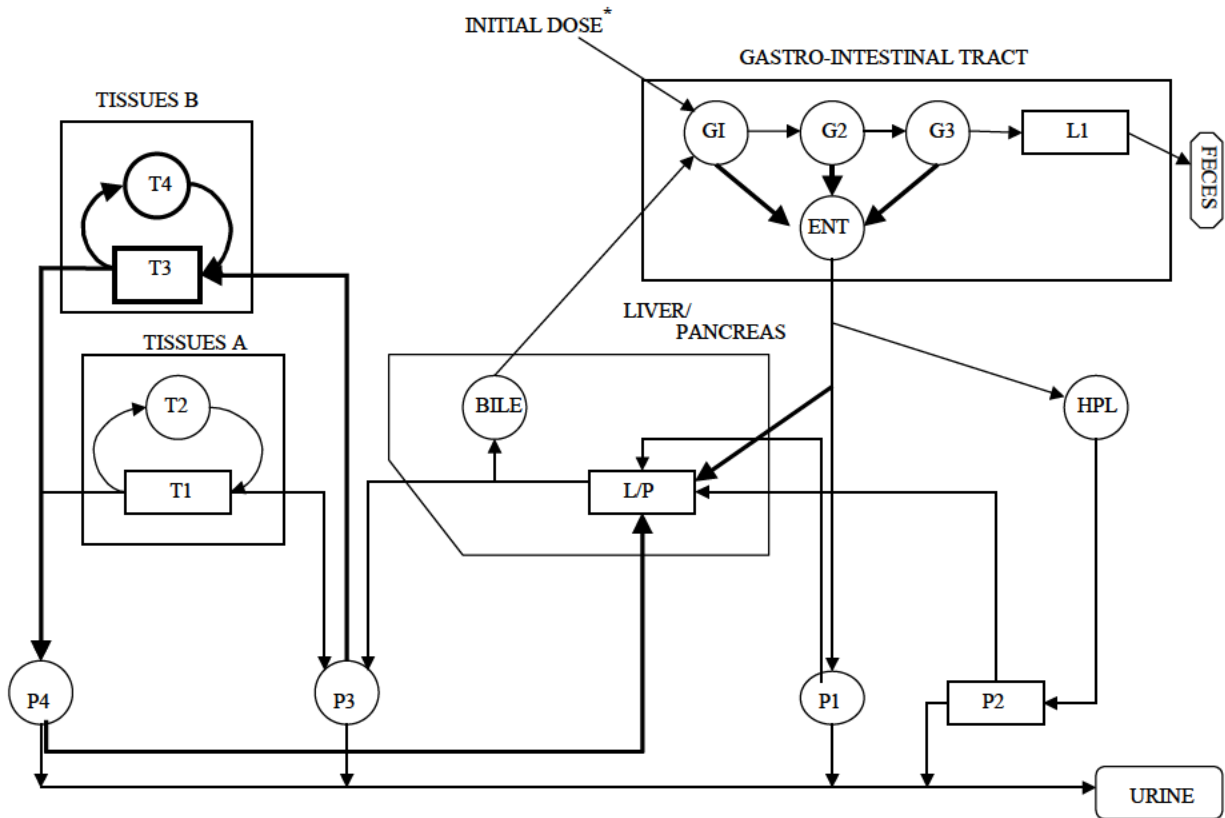
Swanson et al. (1991) Selenomethionine Model

Description of the model. Swanson and coworkers (Patterson et al. 1993; Swanson et al. 1991) produced a model for ingested selenomethionine in adult humans based on data from human subjects who consumed a single oral dose of $200\text{ }\mu\text{g }^{74}\text{Se}$ as selenomethionine and the model of the kinetics of ingested selenite described above. Four major changes (indicated by bold lines in Figure 3-9) were made to the selenite model to achieve an adequate fit to the selenomethionine data: (1) the amount of label absorbed into the enterocyte was increased (the absorption of ^{74}Se was 98% for selenomethionine compared with 84% for selenite), (2) the amount of label removed from the plasma in the first pass through the liver was increased, (3) a pathway from P4 back to the liver was added, providing for conservation and reutilization of amino acids (estimated 95% of material from P4 is recycled), and (4) a second tissue subgroup was added to the model and rate constants were adjusted so that the subgroups had different turnover times.

The most important differences between the selenite and selenomethionine models lie in the turnover times. The estimated turnover times in the plasma, liver/pancreas, and tissues are shorter for selenomethionine than for selenite, but the estimated turnover time for the whole body is more than twice as long for selenomethionine as for selenite. This is probably because selenite is not recirculated, whereas selenomethionine is extensively recycled, passing through the individual organs and tissues many times before being excreted.

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Figure 3-9. Selenomethionine Model, a Kinetic Model for Selenomethionine Metabolism



The arrow with an asterisk indicates the site of the oral Se tracer. Arrows between compartments represent pathways of fractional transport. Compartments depicted as rectangles represent delays. G1, G2, G3, three-gut compartments, probably small intestine; ENT, enterocytes (intestinal cells); HPL, compartment in hepatopancreatic subsystems or lymphatic system; L/P, liver and pancreas; L1, large intestine; T1, T2, T3, T4, peripheral tissues, e.g., skeletal muscle, bone, kidney. Feces and urine along the gastrointestinal tract, enterohepatic recirculation, four-kinetically distinct plasma pools, P1–P4, a subsystem consisting of the liver and pancreas, two tissue subsystems that are slowly turning-over, and a pathway for reutilization of selenium metabolites from peripheral tissues. The bold lines indicate the major modifications to the Selenite Model (Figure 3-8).

Source: Patterson et al. 1993

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Validation of the model. The extent to which this model has been validated is not described by the authors (Patterson et al. 1993; Swanson et al. 1991).

Risk assessment. The model was designed to simulate the pharmacokinetics of selenium orally administered as selenomethionine to humans as a preparation for a larger anti-cancer supplementation study jointly undertaken by the NCI and the USDA (Patterson et al. 1993; Swanson et al. 1991).

Target tissues. The model is designed to simultaneously account for the appearance and disappearance of selenium in plasma, urine, and feces after administration of a single oral dose of ^{74}Se as selenomethionine (Patterson et al. 1993; Swanson et al. 1991).

Species extrapolation. The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation. The model is designed to simulate oral exposures to selenomethionine and cannot be applied to other routes of exposure without modification.

Extrapolation to other forms of selenium. The model is designed to simulate oral exposures to selenomethionine and cannot be applied to other forms of selenium without modification.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

As discussed in Section 3.4.1, selenium is readily absorbed by inhalation or ingestion when present in any of several compounds. Inhalation and oral absorption are extensive, although the rate of absorption varies depending on the form of selenium (Medinsky et al. 1981a; Moser-Veillon et al. 1992; Swanson et al. 1991; Weissman et al. 1983; Young et al. 1982). Oral bioavailability is generally independent of the exposure level, but may be increased in some selenium-deficient individuals (Griffiths et al. 1976; Martin et al. 1989a; Thomson 1974; Thomson et al. 1977). Selenate and selenomethionine appear to be absorbed by the intestine largely unchanged, while selenite and selenocysteine are metabolized during absorption (Hasegawa et al. 1995, 1996b; Spencer and Blau 1962; Whanger et al. 1976, 1996). No evidence of significant dermal absorption of selenium by humans was located, although mice can absorb topically-applied selenomethionine (Burke et al. 1992b). An active transport mechanism for selenomethionine

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absorption in the intestine has been described (Spencer and Blau 1962), but mechanisms of absorption and distribution for dermal and pulmonary uptake are unknown and subject to speculation.

Absorbed selenium is carried throughout the body in the blood, eventually being distributed to all tissues. Injection studies in humans have shown that after selenium enters the blood, it rapidly becomes protein-bound (Burk 1974; Hirooka and Galambos 1966a), while *in vitro* studies have shown that selenite is accumulated in erythrocytes via an active transport mechanism (Lee et al. 1969). Selenium is an essential element and is incorporated into selenoproteins (e.g., glutathione peroxidase, iodothyronine deiodinases) as selenocysteine. Most studies report similar distribution patterns for selenium, regardless of the form in which it was administered; however, the concentration reached is generally higher for doses delivered as an organic form of selenium, such as selenomethionine, than for the same dose delivered as an inorganic form (Behne et al. 1991; Butler et al. 1990; Grønbaek and Thorlacius-Ussing 1992; Ip and Hayes 1989; Salbe and Levander 1990b; Shiobara et al. 1998; Zi-Jian Jie 1992). In humans, the highest levels of selenium are found in the liver and kidney (see Table 3-6 for normal levels of selenium in human tissues). Selenomethionine is not synthesized by humans, but can be incorporated into proteins in the place of methionine; because of this, selenomethionine is retained for a longer time within the body than inorganic forms, and it may therefore represent a storage form of the element. Unlike selenomethionine, there is no evidence that selenocysteine and inorganic selenium (selenate) are incorporated non-specifically into plasma protein, suggesting that these forms are metabolized by specific selenium metabolic processes. For example, selenocysteine seems to incorporate selenium into selenoproteins, but not into other proteins in place of cysteine (Burk et al. 2001).

Selenium and the glutathione (GSH) system have key functions in the body's antioxidant defense (Arteel and Sies 2001; Brigelius-Flohe 1999). GSH is involved in direct interception of pro-oxidants, as well as the reduction of other antioxidants from their oxidized forms (Arteel and Sies 2001). GSH also has ancillary functions (e.g., metabolism, cell signaling, and protein interactions) that can mediate defense against antioxidants. The redox reactions of GSH involve glutathione peroxidase (GPX) and glutathione disulfide (GSSG) as catalysts, whereas the main class of enzymes involved in thioether formation are the GSH transferases. Antioxidant protection by selenium in the mammalian cell is mediated by selenoamino acids, either as selenocysteine or selenomethionine. Selenomethionine has GPX-like activity, and the active site of GPX contains selenocysteine residues. GPX catalyzes the reduction of various kinds of hydroperoxides (e.g., simple hydroperoxides, lipid peroxides) by using GSH as the reducing substrate. Several isozymes of GPX have been identified, including plasma GPX, gastrointestinal GPX, and phospholipid hydroperoxide GPX (reduces lipid hydroperoxides found in biomembranes and sperm)

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(Brigelius-Flohe 1999). Other selenoproteins (e.g., selenoprotein P and thioredoxin reductase) also have been shown to have antioxidant properties, and can function in the defense against peroxynitrite, by reducing this oxidizing and nitrating species into nitrite (Arteel and Sies 2001; Holmgren and Kumar 1989; Burke and Hill 2000; Ganther 1999).

The antioxidant action of GPX towards hydroperoxides appears to involve an enzymatic catalysis reaction cycle (a 'tert-uni ping-pong' mechanism) (Arteel and Sies 2001). The reaction cycle is thought to proceed in three main steps, involving the enzyme-bound selenocysteine, which is present as the selenol. In the first step of the reaction, the organic hydroperoxide reacts to yield selenenic acid and the corresponding alcohol. The remaining steps consist of the sequential reduction by thiols (GSH), leading to regeneration of the selenol and glutathione disulfide. GPX serves more as an ancillary reductant than as a direct antioxidant *per se*.

Deiodination is an important mechanism for the deactivation of the thyroid hormones, T_4 and T_3 , as well as for the production of extrathyroidal thyroid T_3 . The deiodination reactions are catalyzed by selenium-dependent deiodinase enzymes (selenodeiodinases). Three selenodeiodinases have been described that differ in substrate preference, reaction products, response to inhibitors, and response to T_3 (Larsen et al. 1998). Full activity of each enzyme requires selenocysteine in the amino acid sequence of the active site, which is the basis for deiodination activity being responsive to nutritional selenium status (see Section 3.9).

Excretion of selenium by humans occurs in the urine, feces, expired air, and sweat, but urine and feces are the major routes of elimination. Some of the selenium in feces may be due to biliary excretion (Levander and Baumann 1966a, 1966b). Elimination is reduced in selenium-deficient individuals and may represent a mechanism by which selenium levels are regulated (Martin et al. 1989a; Swanson et al. 1991).

Methylation is an important mechanism of detoxification for selenium; dimethyl selenide is exhaled, and the trimethylselenonium ion is the major urinary metabolite of selenium. Experiments in mice suggest that the hepatic toxicity of selenium may be at least partly due to depression of selenium methylation in the liver, resulting in the accumulation of excess selenides (Nakamuro et al. 2000).

3.5.2 Mechanisms of Toxicity

Selenium in the body can be grouped in three main categories: selenium in proteins, non-protein selenium species, and selenoamino acids (Lobinski et al. 2000). The most prevalent selenium species

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include selenocysteine, selenomethionine, and inorganic forms of selenium (selenite and selenate). Selenocysteine-containing proteins are particularly important because they are largely responsible for the antioxidant properties of selenium. The main selenoproteins are glutathione peroxidase (GPX), thioredoxin reductase, and iodothyronine 5'-deiodinases, and the activity of these selenocysteine enzymes generally decreases and increases when selenium is depleted or repleted (Lobinski et al. 2000). Selenium can also be incorporated directly into non-specific proteins in the place of methionine (i.e., as selenomethionine), which contributes to the pool of selenomethionine-rich proteins present in human and animal tissues, or become part of selenium-binding proteins in which selenium is not covalently bound to the molecules (Arteel and Sies 2001; Bansal et al., 1989, 1990; Gladyshev and Kryukov 2001; Lobinski et al. 2000; Sani et al., 1988).

Little is known about the specific biochemical mechanism(s) by which selenium and selenium compounds exert their acute toxic effects. Generally, water-soluble forms are more easily absorbed and are generally of greater acute toxicity. Several mechanisms have been proposed to explain the various long-term toxic effects of excess selenium, such as alterations in the hair, skin, nails, liver, thyroid, and nervous system, as discussed below. This includes information on mechanisms by which selenium exerts effects as a component of GPX, thioredoxin reductase, and the iodothyronine deiodinases, although the roles of other selenium-containing proteins in mammalian metabolism have not been clarified. Selenium also has strong interactions with other nutrients such as vitamin E, toxic metals such as mercury and cadmium, and various xenobiotics (see Section 3.9).

Selenium readily substitutes for sulfur in biomolecules and in many biochemical reactions, especially when the concentration of selenium is high and the concentration of sulfur is low in the organism (Stadtman 1983; Raisbeck 2000). Inactivation of the sulfhydryl enzymes necessary for oxidative reactions in cellular respiration, through effects on mitochondrial and microsomal electron transport, might contribute to acute selenium toxicity (Levander 1982; Lombeck et al. 1987; Mack 1990; Shamberger 1981). Selenium may have a role in hepatic heme metabolism that is related to GPX or lipid peroxidation (Levander 1982). Selenocysteine is specifically found in some proteins (e.g., glutathione peroxidase); selenomethionine appears to randomly substitute for methionine in protein synthesis. This appears to be an additional mechanism for intermediate- or chronic-duration toxicity (Levander 1982; Stadtman 1983; Tarantal et al. 1991). Skin, hair, and nail damage are significant indicators of chronic selenium overexposure. The mechanism causing these integumentary effects is unclear, but could be related to the high selenium concentrations in these tissues as a consequence of the substitution of selenium for sulfur in certain amino acids, including the disulfide bridges that provide tertiary structure and function to

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proteins. For example, substitution of selenium for sulfur in keratin results in weakened physical protein structure and failure of keratinized tissues such as hair and hoof (Raisbeck 2000). The nails and hair are considered to be routes for excretion of excess selenium (Yang et al. 1989b).

Considerable evidence is available supporting oxidative stress as the key biochemical lesion of selenium intoxication (Raisbeck 2000; Spallholz et al. 1994). Inorganic forms of selenium appear to react with tissue thiols by redox catalysis resulting in formation of reactive oxygen species (superoxide anion $[O_2^-]$). For example, selenite is a prooxidant catalyst that reacts with GSH endogenously in cells or extracellularly causes toxicity by the formation of superoxide and elemental selenium (Seko and Imura 1997; Seko et al. 1989; Spallholz 1994). Selenocystamine (a diselenide) catalyzes the formation of superoxide under aerobic conditions in the presence of thiol; this reaction could play a role in the toxicity of diselenides and alkylselenols (Chaudiere et al. 1992). Selenium can have inhibitory effects on thiol proteins by modification via (1) formation of S-Se-S (selenotrisulfides) and S-Se (selenylsulfide) bonds, (2) catalysis of S-S (disulfide bonds) with no incorporation of selenium in the protein, and (3) formation of Se-Se diselenides (Ganter 1999). Proteins that contain regulatory cysteines can similarly form selenium adducts with toxicity resulting from inactivation of essential thiol groups.

Selenium can also play a role in the redox-regulating activities of GPXs with inflammatory superoxides and phospholipid hydroperoxides. A selenoprotein P-supported plasma GPX could bind to endothelial cells and protect them against inflammatory hydroperoxides (Hill and Burke 1989, 1997). Metabolites from reactions of GPX and phospholipid hydroperoxides could suppress cytokine or growth factor triggered gene activation (Flohe et al. 1997). Selenium appears to be a key element that, through its modulation of GPX activity, can inhibit activation of the transcription factor NF- κ B, which is involved in the regulation of the expression of numerous cellular genes, particularly those involved in immune, inflammatory, and stress responses (Kretz-Remy and Arrigo 2001).

Apoptosis induced by tumor necrosis factor might be inhibited by overexpression of cytosolic GPX or phospholipid hydroperoxide GPX because the apoptotic signaling cascade could be stimulated by hydroperoxides (Brigelius-Flohe 1999). Selenium compounds that form the methylselenide anion (selenol) have been shown to induce cellular apoptosis, and one selenium compound, selenium-methylselenocysteine, induced apoptosis in cancer cells through activation of capsases (a likely mechanism for other selenium compounds that also induce apoptosis) (Ganter 1999; Spallholz 2001). Hypotheses for the protective role of selenium against cancer development include the inhibition of carcinogen-induced covalent DNA adduct formation, retardation of oxidative damage to DNA, lipids, and proteins, and

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modulation of cellular and molecular events that are critical in cell growth inhibition and in the multi-step carcinogenesis process (El-Baoumy 2001; Ganther 1999; Spallholz 2001).

Intracellular redox function can also be affected by selenium deficiency. In general, the toxicity of compounds that are metabolized to form free radicals increases in selenium-deficient animals, and many of the effects are prevented by supplements of selenium. For example, the active role of selenium in thioredoxin reductase helps reduce nucleotides in DNA synthesis, and selenium in GPX reduces phospholipid hydroperoxides and hydrogen peroxide (Ganther 1999; Holmgren and Kumar 1989; Spallholz 2001). Peroxidative degradation of polyunsaturated fatty acids in membranes causes formation of chemicals, such as free radicals, aldehydes, and epoxides, which can have cytotoxic, hepatotoxic, and genotoxic effects (Esterbauer et al. 1989). The role of selenium in protecting against early pregnancy loss may be linked to reduced antioxidant protection of biological membranes and DNA by low concentrations of GPX. Levels of hemoglobin adducts from aldehydes and epoxides in selenium-deficient animals were enhanced due to loss of selenium-dependent GPX activity (Kautiainen et al. 2000). Degenerative diseases such as skeletal and cardiac myopathies, which occur particularly in selenium-deficient cattle and sheep, appear to be due to loss of membrane phospholipid hydroperoxide GPX activity (Arthur and Beckett 1994b).

Selenium status can also influence thyroid hormone function via the deiodinase enzymes (Brätter and Negretti De Brätter 1996; Hawkes and Turek 2001). Selenium is a critical component of the deiodinase enzymes, including iodothyronine 5'-deiodinases, which convert the prohormone thyroxine (T_4) to the active circulating form, triiodothyronine (T_3) (Delange 2000; Köhrle 1994; St Germain and Galton 1997). Selenium is also a component of GPX, the main enzyme responsible for protecting thyroid cells against oxidative damage. GPX is involved in the detoxification of hydrogen peroxide, which is produced in the thyroid during the conversion of T_4 to T_3 .

3.5.3 Animal-to-Human Extrapolations

No studies were located that specifically examined species-related differences in selenium pharmacokinetics. Similar patterns of absorption, distribution, and elimination have been reported for human and animal systems and the dermal, endocrine, and neurological effects of chronic exposure in humans are similar to those reported for animals exposed to very high doses of selenium. However, species-specific differences in toxicity are present (e.g., the main effect of selenium toxicity in rodents is

damage to the liver, which is not observed in humans) and this may represent evidence of underlying differences in how selenium is metabolized.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for “...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...”. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones (Köhrle 1994; St. Germain and Galton 1997). The deiodinases

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contain a selenocysteine at the active site, which is required for catalytic activity. There are three types of deiodinases and they differ in terms of tissue distribution, reaction kinetics, efficiency of substrate utilization, and sensitivity to inhibitors. The first to be recognized as a selenoprotein was type I iodothyronine 5'-deiodinase, which converts the prohormone thyroxine (T_4) to the active form, triiodothyronine (T_3) and to date, studies of the effects of excess selenium have focused on this protein. Under normal circumstances, the human thyroid produces only 20–30% of its hormone as T_3 ; the remainder is T_4 (a minute amount of reverse T_3 (rT_3) is also produced), which is largely converted to active T_3 by type I deiodinase located within the liver, euthyroid pituitary, kidney, thyroid, and brain. Type I deiodinase is a membrane bound protein and, thus, its activity has not been directly measured in studies of humans supplemented with selenium. Human studies have instead measured serum levels of T_3 , rT_3 , T_4 , and TSH.

Two human studies have demonstrated a decrease in T_3 levels in response to increased dietary selenium although the hormone levels remained within the normal human range (Brätter and Negretti De Brätter 1996; Hawkes and Turek 2001). The effect of increased dietary selenium on other thyroid hormones is unclear. No significant correlation between selenium intake and serum T_4 or TSH levels was found in the study of Brätter and Negretti De Brätter (1996), although Hawkes and Turek (2001) showed that TSH concentration increased (+37%) and was significantly different relative to baseline levels ($p < 0.06$) in a high selenium group. In a third study of the effects of selenium supplementation, New Zealanders with normally low selenium intake (unsupplemented intake of 28–29 $\mu\text{g/day}$) showed a reduction in T_4 concentration in all groups after 20 weeks (Duffield et al. 1999). A significant inverse correlation was found between serum levels of selenium and TSH among fish consumers; however, it is not known if this population had a high selenium intake (Hagmar et al. 1998).

Male rats receiving diets supplying 0.05mg selenium/kg/day for 6–12 weeks have been shown to have reductions in type-I-deiodinase activity (Behne et al. 1992; Eder et al. 1995; Hotz et al. 1997). However, the levels of thyroid hormones in these animals have not shown a consistent pattern. Exposure to 0.055 mg selenium/kg/day as sodium selenite for 40 days produced a significant decrease in serum levels of T_3 (Eder et al. 1995). In another study, a dose of 0.09 mg selenium/kg/day as sodium selenate in food for 6 weeks produced a significant (~30%) increase in TSH (Hotz et al. 1997), and no significant changes in thyroid levels of T_3 or T_4 were found in rats receiving 0.105 mg selenium/kg/day as sodium selenite or 0.118 mg selenium/kg/day as L-selenomethionine for 3 months (Behne et al. 1992).

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Many studies have documented reduced body weight gain in young animals treated with selenium compounds and abnormal weight loss in older animals (Grønbaek et al. 1995; Halverson et al. 1966; Harr et al. 1967; Jacobs and Forst 1981a; Nelson et al. 1943; NTP 1994; Johnson et al. 2000; Palmer and Olson 1974; Panter et al. 1996; Schroeder 1967; Tsunoda et al. 2000). There is evidence to suggest that these effects may be due in part to the interactions of selenium or selenium compounds with hormones that regulate normal growth and body weight. Reduced insulin-like growth factor-binding protein-3, growth hormone secretion in response to growth hormone releasing factor, and somatomedin C levels have been reported in rats exposed to sodium selenite in drinking water (Grønbaek et al. 1995; Thorlacius-Ussing et al. 1988), although somatomedin C was not a sensitive end point in humans from a high selenium area of South Dakota (Salbe et al. 1993).

No studies were located regarding adverse effects on human reproduction following oral exposure to elemental selenium or to selenium compounds. However, data from animal studies suggest that oral exposure to selenium may be associated with male infertility. Adverse effects associated with selenium exposure include decreased sperm counts in rats and rabbits (El-Zarkouny et al. 1999; Kaur and Parshad 1994; NTP 1994), sperm abnormalities in rats and rabbits (El-Zarkouny et al. 1999; Kaur and Parshad 1994), testicular hypertrophy in rats (Turan et al. 1999a), and a significant reduction in serum testosterone in rabbits (El-Zarkouny et al. 1999). However, it is not clear what effect, if any, this had on the ability of the animals to reproduce, as chronic administration of selenate did not affect male fertility in rats or mice (Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b).

Chronic exposure of mice and rats to otherwise nontoxic doses has been shown to reduce fertility and to markedly reduce the viability of the offspring of pairs that are able to conceive (Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b). Selenium exposure has been shown to alter the length of the estrous cycle in female mice (Nobunaga et al. 1979) and to alter the menstrual cycle in monkeys (Cukierski et al. 1989). Vaginal cytology of female rats provided with drinking water containing selenate or selenite indicated that the rats spent more time in diestrus and less time in proestrus and estrus than the controls (NTP 1994). However, it is not clear what effect, if any, this had on the ability of the animals to reproduce.

Fertility studies in mice, rats, and pigs have demonstrated reduced rates of conception after oral treatment with selenium as selenate or selenite (Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b). Decreased conception rates and increased resorption rates have been reported for cattle, sheep, and horses fed diets naturally containing organic selenium compounds and

exhibiting symptoms of selenosis (Harr and Muth 1972). An increased concentration of progesterone in the milk and an association of cystic ovaries with elevated blood selenium concentrations was observed in cows receiving selenium supplementation (Mohammed et al. 1991).

Other possible examples of endocrine disruption due to selenium exposure include pancreatic damage in sheep and rats fed selenium as sodium selenite, sodium selenate, or seleniferous wheat (Halverson et al. 1966; Harr et al. 1967; Smyth et al. 1990) and decreased plasma glucose (an insulin-like effect) in rats injected with sodium selenate. However, these are isolated reports and it is not clear what relevance they have for selenium toxicity in humans.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are

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proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Selenium is known to be an essential micronutrient for humans and animals; therefore, inadequate as well as excessive selenium intake can cause adverse health effects. The Food and Nutrition Board of the National Research Council has established adequate intakes (AI) of 15–20 µg/day for infants based on the selenium content of milk of well nourished, but unsupplemented, mothers (NAS 2000). No data were available on which to base RDAs for children or adolescents; thus, the RDAs for children and adolescents are extrapolated from adult values. Studies of selenium deficient populations suggest that children are more susceptible to the effects of selenium deficiency and have the highest need for selenium of any individuals in the population (Chen et al. 1980; Yang et al. 1988). Premature and full-term infants generally have significantly lower blood selenium levels than their mothers and/or normal adults (Gathwala and Yadav 2002). Infants born prematurely have lower hepatic selenium stores than term infants at birth, indicating that premature infants are at particular risk for the development of a deficiency state if adequate selenium is not provided in the diet (Bayliss et al. 1985).

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Limited information is available relevant to the toxicity of selenium in children. Observations from the early literature, particularly in livestock and chickens, suggest that young animals are less resistant to selenium than older ones (NAS 1976a; Rosenfeld and Beath 1964b), and a study in rats found that weanlings accumulated more selenium in their tissues than adults (Salbe and Levander 1989). In contrast, the available information in humans suggests that children may be less susceptible to toxic effects of selenium than adults. Most data come from children living in areas of chronic high dietary selenium intake (Yang et al. 1989a, 1989b). Children (aged 3–12 years) in a seleniferous area of China were found to have a significantly higher intake of selenium than the adults in their community, but a corresponding increase in blood levels of selenium appeared only in the children aged 7–12. When the incidence of selenosis in different age groups was examined, it was found that 97% of cases were older than 18 years, and no cases were observed in children below 12 years of age, even though selenium intakes per kg body weight and blood selenium levels in these age groups were found to be either higher than or equal to those of affected adults. One study of children living in a seleniferous area of Venezuela found a significant increase in the percentage of children showing lower than normal height compared with controls from a nonseleniferous area (Brätter et al. 1991a). However, these children also had very low intakes of zinc compared with controls (10–25% of controls), and it is likely that their reduced growth rate is due to inadequate intake of zinc. Another study that compared children from seleniferous and non-seleniferous areas of Venezuela found slightly reduced height, weight, hemoglobin levels, and hematocrit values for the children from the seleniferous area (no statistical analysis was performed), although no clinical signs of selenosis were observed (Jaffe et al. 1972). However, the children from the seleniferous zone had a poorer diet, consumed less milk and meat, and had a greater incidence of intestinal parasites, which may account for the differences observed.

No adverse developmental effects of excess selenium have been reported for humans. Excess selenium is a demonstrated teratogen in birds (Franke and Tully 1935; Franke et al. 1936; Gruenwald 1958; Khan and Gilani 1980; Palmer et al. 1973), but there is no clear evidence linking selenium exposures to developmental effects in mammals. Malformations have been reported for livestock that consumed naturally high seleniferous diets (Dinkel et al. 1963; Rosenfeld and Beath 1964), but it is not clear that these reports took into account consumption of other toxic range plants. Other studies of developmental effects in livestock receiving controlled diets with known amounts of selenium have generally not observed abnormalities, reduced birth weights, or increased mortality (Panter et al. 1995; Yaeger et al. 1998). Likewise, studies of laboratory animals have not observed developmental effects, except at levels of selenium administration that produce maternal toxicity (Bergman et al. 1990; Chiachun et al. 1991; Ferm et al. 1990; NTP 1996; Poulsen et al. 1989; Rosenfeld and Beath 1954; Schroeder and Mitchener 1971b; Thorlacius-Ussing

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1990). In a teratology study of long-tailed macaques, no gross abnormalities or growth retardations were observed in fetuses from mothers administered doses that produced maternal toxicity.

No studies were located that compared pharmacokinetic properties of selenium in humans or animals of different ages. Selenium is transferred to fetuses via the placenta (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Jandial et al. 1976; Mahan and Kim 1996) and to infants via breast milk (Brätter and Negretti De Brätter 1996; Brätter et al. 1991b; Li et al. 1999; Michalke and Schramel 1998; Moser-Veillon et al. 1992; Rodríguez Rodríguez et al. 1999; Viitak et al. 1995; Yang 1989b). Studies of lactating women have shown a clear relationship between levels of selenium in the mother's diet and the concentration of selenium in her breast milk (Brätter et al. 1991b). Colostrum contains more than twice the selenium concentration of mature human milk, but the selenium content of mature milk changes little with advancing stages of lactation (Gathwala and Yadav 2002; Higashi et al. 1983; Mannan and Picciano 1987; Smith et al. 1982). No information was located regarding adverse effects in infants breast-fed by mothers in regions with high selenium diets.

A series of conditions are associated with oxygen therapy in neonates, including bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, patent ductus arteriosus, and neuronal injury in hypoxic ischemic encephalopathy (Gathwala and Yadav 2002). Because these effects might be caused at least in part by oxygen radicals, it has been suggested there is an "oxygen radical disease" in neonatology. This indicates that antioxidants may form an important modality of treatment in neonates, and because selenium is part of the antioxidant enzyme glutathione peroxidase, good selenium nutrition is important for antioxidant defense (Gathwala and Yadav 2002).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in

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readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to selenium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by selenium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Selenium

Biomarkers of exposure are available for high and low exposures to selenium. Selenium can be detected in the blood, feces, urine, hair, and nails of exposed individuals. Both selenium deficiency and excessive levels of selenium are associated with several disorders. For purposes of comparison, reported mean selenium concentrations in whole blood, blood constituents, urine, hair, nails, and the placenta for healthy individuals living in the United States and several other countries are listed in Table 3-7. Based on information collected from 1988 to 1994 in the third National Health and Nutrition Examination Survey (NHANES III), the serum concentration of selenium in the U.S. population has been estimated by sex and

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age (DHHS 1997). The mean selenium serum concentration for all ages and both sexes was estimated to be 0.125 mg/L. Additional results from NHANES III are summarized in Chapter 6 (Section 6.5, Table 6-6). The analytical methods used to measure selenium (described in Chapter 7) have improved, and the more recent studies may be more reliable. The values for the Chinese populations studied by Yang et al. (1983, 1989b) were those reported for individuals living in the selenium "adequate" regions included in the study. "Normal" selenium concentrations in blood constituents and other tissues in people from some countries (e.g., New Zealand) are generally lower than those in people living in the United States. In general, urinary excretion rates of 20–200 µg selenium/day are not associated with either selenium deficiency or toxicity (Sanz Alaejos and Diaz Romero 1993).

In the United States and other developed countries, hair selenium concentrations are not necessarily indicative of dietary exposure to environmental selenium. Users of therapeutic dandruff shampoos containing selenium sulfide may have high levels of selenium in their hair because the externally deposited selenium adsorbs to hair (Alfthan 1985). However, due to minimal levels of dermal absorption of selenium from shampoo, blood and urine levels are not significantly affected by selenium-containing shampoos (Howe 1979). Toenail samples have also been used as biomarkers of selenium exposure (Hunter et al. 1990a). Selenium levels in toenails were measured in volunteers who ate bread containing selenium for 1 year (Longnecker et al. 1993). During this time period, selenium in the large toenail did not reach a steady state, while a steady state was reached in the other toenails. After conclusion of the 1-year exposure, levels of selenium continued to decline until they reached baseline levels in 2 years.

Below plasma and whole blood selenium concentrations of 0.10 mg selenium/L, a positive correlation has been reported between blood selenium levels and both erythrocyte and whole blood GPX activity (Duffield et al. 1999; Perona et al. 1977; Thomson 1977; Valentine et al. 1988). GPX is an enzyme that acts as a scavenger of peroxides and protects cells from oxidative damage. However, whole blood selenium levels ≤ 0.10 mg selenium/L represent the lower end of the range of whole blood selenium concentrations reported by Allaway et al. (1968) for American males.

A correlation between blood selenium levels and GPX activity was not observed when plasma and whole blood selenium levels were above 0.10 mg selenium/L. Therefore, GPX activity is likely to be a biomarker for selenium deficiency but not for overexposure. Neve et al. (1988), on the other hand, found no relationship between erythrocyte or plasma GPX activity levels and plasma selenium levels in a group of Belgian subjects with plasma selenium levels between 0.087 and 0.13 mg selenium/L. However, platelet GPX activity levels did correlate with plasma selenium levels within this range (Neve et al. 1988).

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Valentine et al. (1980) measured the level of selenium in whole blood, urine, and hair of 33 residents from a Mexican village who consumed drinking water contaminated with selenium (0.026–1.8 mg selenium/L) from a uranium mill tailing pond. Blood levels ranging from 0.133 to 0.248 mg selenium/L, urine excretion rates ranging from 14.4 to 337.5 µg selenium/day, and hair selenium levels ranging from 0.02 to 1.98 µg selenium/g were not correlated with GPX activity. In examining the relationship between selenium and GPX activity, selenium-dependent GPX activity must be distinguished from nonselenium-dependent GPX activity (Edwards and Blackburn 1986).

Selenoprotein P, which contains 10 selenocysteines, is the principal selenoprotein found in plasma (Sunde 1990). Selenoprotein P in plasma also does not continue to increase with increasing selenium and has been suggested as an alternative to GPX as a biomarker for selenium status (Duffield et al. 1999; Huang et al. 1995). The function of selenoprotein P has still not been determined.

Field studies have used primarily blood or urine levels to indicate the degree of selenium exposure. Valentine et al. (1978) found a significant correlation between selenium levels in well water used for drinking and urine selenium excretion measured for 35 residents in a New Mexico community. However, no correlation was found between selenium levels in well water and the blood selenium levels of the 35 residents (Valentine et al. 1978). The correlation coefficients between the log of urine-selenium excretion (µg selenium/day) and the log of blood-selenium (mg selenium/L) with the log of the well water selenium concentration (mg selenium/L) were 0.57 ($p < 0.01$) and 0.14 ($p > 0.05$), respectively. The correlation coefficient between the log of hair selenium concentration (µg selenium/g) and the log of the well water selenium levels (mg selenium/L) was 0.45 ($p < 0.01$).

Methylation is a detoxification pathway for selenium, and the extent of methylation is dose-dependent. Monomethylated selenium is excreted in the urine at deficient, normal, and low-toxic levels of selenium, and excretion of trimethylated selenium increases at toxic doses (Kobayashi et al. 2002). The main monomethylated form of selenium has been identified as a selenosugar (1β-methylselenol-*N*-acetyl-D-galactosamine). The dose-dependent nature of the metabolism indicates that urinary monomethylated (selenosugar) and trimethylated selenium could be used as indicators of selenium exposure that increase within the required to low-toxic range and with a distinct toxic dose, respectively (Kobayashi et al. 2002).

Clinical symptoms have been associated with excessive blood, urine, and hair levels of selenium in exposed patients. Glover (1967) examined workers in a selenium rectifier factory and found that selenium levels in urine from workers exposed to selenium (annual averages from 1954 and 1958 range

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from 0.076 to 0.109 mg selenium/L urine) were higher than the average urine selenium levels of preemployment applicants (average, 0.034 mg selenium/L urine; range, 0–0.15 mg selenium/L). Garlic breath, skin rashes, indigestion, lassitude, and irritability were noted, but no increase in mortality among exposed workers was detected. Smith and Westfall (1937) examined urine selenium levels in rural populations in Wyoming, South Dakota, and Nebraska and reported evidence of skin discoloration and lesions, tooth decay, diseased nails, gastrointestinal disturbances, and arthritis in individuals with urine selenium levels of 0.2–1.98 mg selenium/L; however, the authors did not find a significant correlation between clinical signs and the level of selenium in the urine. Longnecker et al. (1991) examined ranchers in the same area of the United States where selenosis of livestock had been observed. No clinical effects were observed with concentrations up to 2.2 mg/L in urine. Yang et al. (1983, 1989a, 1989b) measured mean blood, urine, and hair selenium levels of 3.2 mg selenium/L, 2.68 mg selenium/L, and 32.2 µg selenium/g, respectively, in a high selenium area where chronic selenosis was common in China. The clinical signs of selenium intoxication included loss of hair and nails, skin lesions, tooth decay, and nervous system disorders. In another area of China with high environmental levels of selenium but no signs of chronic selenosis in the population, blood selenium levels averaged 0.44 mg selenium/L (with a range from 0.35 to 0.58 mg selenium/L).

At blood levels of 0.06–0.20 mg selenium/L, Deguchi (1985) found selenium to be positively correlated with grasping power and blood pressure in normal men and women and with hematocrit and hemoglobin concentrations in normal women. Similar correlations were not found in subjects with proteinuria or hypertension. In addition, Gebre-Medhin et al. (1988) found that in healthy children, serum selenium levels of 0.055–0.082 mg selenium/L were positively correlated with serum cholesterol, serum triglycerides, low and very low density lipoproteins, and apolipoproteins. Similar correlations were not found in diabetic children, who have slightly elevated serum selenium levels.

Biomarkers of Deficiency. Two endemic diseases, Keshan disease and Kashin-Beck disease, have been reported in selenium-deficient populations in China in which mean hair, blood, and urine selenium levels are low (Yang et al. 1988). Acute Keshan disease, manifested as nausea, vomiting of yellowish fluid, and necrosis of the myocardium, has been found in a population with an average whole blood selenium concentration of 0.018 mg selenium/L, an average urinary concentration of 0.007 mg selenium/L, and an average hair selenium concentration of 0.123 µg/g (Yang et al. 1988). Kashin-Beck disease, which causes atrophy, degeneration, and necrosis of cartilage tissue, was observed in selenium-deficient areas in China, in which the average selenium concentration in hair ranged from 0.077 to 0.165 µg selenium/g and blood selenium concentrations averaged approximately 0.02 mg selenium/L. In nonaffected areas in

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China, the selenium content is $>0.2 \mu\text{g}$ selenium/g in hair and $>0.06 \text{ mg}$ selenium/L in blood (Yang et al. 1988). Although the association between selenium deficiency and Kashin-Beck disease is unclear, selenium-deficiency diseases are unlikely to occur in persons in the United States. If selenium is not added to parenteral nutrition solutions, persons on long-term total parenteral nutrition are at risk for developing selenium deficiency symptoms which include cardiomyopathies, muscle pain, and weakness (Thomson 1991).

There is also some evidence that low serum selenium levels are associated with increased cancer risk, but this is not conclusive (Hojo 1981a; Willett et al. 1983). Salonen et al. (1984) concluded that an increased risk of cancer (a combination of gastrointestinal, respiratory, urogenital, hematologic, dermal, and skeletal cancers) in humans in Finland is associated with serum selenium levels of 0.045 mg selenium/L and below. Virtamo et al. (1987) found that cancer patients in Finland, including individuals with gastrointestinal, respiratory, skin, skeletal, urogenital, and hematological cancers, had slightly but not significantly lower serum selenium levels (mean and standard error of $0.0539 \pm 0.0015 \text{ mg}$ selenium/L) compared with noncancer patients ($0.0553 \pm 0.0005 \text{ mg}$ selenium/L). However, serum selenium is generally an indicator only of very recent selenium status. As such, serum selenium may indicate an effect of cancer (malabsorption or anorexia) rather than a cause (Lockitch 1989; van't Veer et al. 1990).

A deficiency of selenium is also associated with cardiomyopathy (Johnson et al. 1981; Oster et al. 1983). Salonen et al. (1982) noted a statistically significant association between serum selenium concentrations of less than 0.045 mg selenium/L and the adjusted relative risk of coronary death, cardiovascular death, and myocardial infarction. Hojo (1981a) noted that patients with epilepsy had significantly lower urinary selenium levels than controls.

3.8.2 Biomarkers Used to Characterize Effects Caused by Selenium

Specific biomarkers were not found for effects of excess selenium, indicating that better markers of effects are needed at high levels of exposure. Garlic breath is a marker of over-exposure to selenium compounds. However, as other metals that are methylated (e.g., arsenic) also result in garlic odor of the breath, this effect is not a unique marker of selenium over-exposure. Hair and nail effects may be the most frequent effects of overexposure to selenium. Hair becomes dry and brittle and breaks off at the scalp. Nails are also brittle and have white spots and longitudinal streaks, and break off easily (Lockitch

1989). Although these effects may not be specific to selenium, if they are observed, a determination of selenium status may be useful.

Yang et al. (1989b) used increased prothrombin time (increased clotting time), a measure of hepatic damage, as a biomarker for selenium but their interpretation of their observations may be unwarranted. The difference they saw in affected humans was very small (1 second); prothrombin time has not been previously demonstrated to correlate with symptoms of selenosis nor used to detect selenosis; and since the test has not been widely used, the results reported for the small number of affected individuals may be within the range of normal values for the general population or a subpopulation (IRIS 2003).

In humans and in animal studies, high concentrations of selenium have been demonstrated to cause neurological effects. Biomarkers of effect for the neurological system have been reviewed by ATSDR (OTA 1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

A wide variety of interactions of selenium with essential and nonessential elements, vitamins, xenobiotics, and sulfur-containing amino acids have been demonstrated in numerous studies. Selenium has been reported to reduce the toxicity of many metals including mercury, cadmium, lead, silver, and to some extent, copper (Frost 1972; Levander 1982). Most forms of selenium and arsenic interact to reduce the toxicity of both elements (Levander 1977). Because of selenium's role in the antioxidant glutathione peroxidase enzymes, selenium also reduces the toxicity of metals in vitamin E-deficient animals (Diplock et al. 1967).

The interactions of selenium with other elements and compounds are complex and not well understood (Naganuma et al. 1983; NAS 1976a). The degree to which selenium is toxic, is taken up by tissues, or is excreted can be influenced by these interactions. Some of the major interactions of selenium compounds with other elements and compounds are described below.

Arsenic. In general, arsenic antagonizes selenium toxicity (Levander 1977). This effect extends to selenium in sodium selenite and selenate, seleniferous wheat, selenocystine, and selenomethionine (Levander 1977). However, a very pronounced synergistic toxicity exists between arsenic and two methylated selenium metabolites, trimethylselenonium ion and dimethyl selenide (Obermeyer et al.

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1971). One of the more striking demonstrations is the antagonism of arsenic-induced terata in rodents by concomitant selenium exposure (Holmberg and Ferm 1969), and pretreatment of mice with sodium selenite reduced the clastogenic effects of a subsequent dose of sodium arsenite (Biswas et al. 1999b). Moxon et al. (1945) found that arsenic could reduce selenium toxicity when compounds of both elements were injected subcutaneously, thereby indicating that arsenic did more than interfere with the gastrointestinal absorption of selenium. Kamstra and Bonhorst (1953) found that arsenic reduced the excretion of volatile selenium compounds in expired air following the injection of compounds of both elements into rats at acutely toxic levels. Levander and Baumann (1966a) found that the amount of selenium retained in the liver decreased and the amount of selenium appearing in the gastrointestinal tract increased as the dose of administered arsenic was increased. Experiments with rats and guinea pigs with cannulated bile ducts confirmed that arsenic increased the biliary excretion of selenium and that selenium increased the biliary excretion of arsenic (Levander and Baumann 1966b). It has recently been suggested that the mutual reduction in toxicity of arsenic and selenium administered together is due to the formation of an arsenic-selenium compound, seleno-bis(S-glutathionyl)arsinium (Gailer et al. 2000b). This compound was isolated from the bile of rabbits injected with selenium and arsenic and identified by X-ray spectroscopy.

Cadmium. Selenium can antagonize the nephrotoxic and hepatotoxic effects of cadmium in rats (Flora et al. 1982; Lindh et al. 1996; Nehru and Bansal 1996; Stajn et al. 1997), the inflammation, atrophy, and necrosis induced by cadmium in testes of rats (Jones et al. 1997; Mason and Young 1967; Ohta and Imamiya 1986; Wlodarczyk et al. 1995; Yiin et al. 1999), and the cardiotoxicity of cadmium in rats (Jamall et al. 1989). The protective effects are thought to occur as a result of the formation of a selenium-cadmium complex of high molecular weight (Chen et al. 1975; Jamall et al. 1989; Jamba et al. 1997; Ohta and Imamiya 1986).

Fluoride. Fluoride ion may interact with selenium; however, the degree and types of interaction depend upon the chemical form of selenium (i.e., organic or inorganic) and the dose. Moxon and DuBois (1939) reported that fluoride increased the toxicity of selenium in rats at 5 mg fluoride/L in the drinking water of young rats fed a diet containing 11 ppm selenium (0.55 mg selenium/kg/day) as seleniferous wheat. Selenium decreased growth and increased mortality in rats drinking fluoridated water compared to rats drinking deionized water. These results were disputed by Hadjimarkos (1969a) who administered 3 mg selenium/L as sodium selenite (0.15 mg selenium/kg/day) either with or without 50 mg fluoride/L as sodium fluoride in the drinking water of rats. The growth and mortality data indicated that the combined administration of selenium and fluoride under the conditions used did not increase selenium toxicity.

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However, the amount of administered fluoride was significantly higher and the amount of administered selenium was significantly lower in the Hadjimarkos (1969a) study than the amounts administered by Moxon and DuBois (1939). No additional studies were located that reexamined the possible interaction between fluoride and selenium.

Iodine. Selenium and iodine interact to affect thyroid function. There are at least two aspects to this interaction. First, selenium is an important component of the deiodinase enzymes, including iodothyronine 5'-deiodinases, which convert the prohormone thyroxine (T_4) to the active circulating form, triiodothyronine (T_3) (Delange 2000; Köhrle 1994; St Germain and Galton 1997). Second, selenium is also a component of GPX, the main enzyme responsible for protecting thyroid cells against oxidative damage. Hydrogen peroxide (H_2O_2) is produced in the thyroid during the conversion of T_4 to T_3 and is detoxified by GPX. An apparent consequence of interaction between iodine and selenium has been observed in human populations deficient in iodine. In some iodine-deficient geographic regions, a reversible hypothyroidism with goiter formation (myxedematous cretinism) is observed (Goyens et al. 1987; Vanderpas et al. 1990). In other iodine-deficient areas, hypothyroidism is accompanied by thyroid cell necrosis. The thyroid cell necrosis appears to result in populations that are deficient in both iodine and selenium (Contempré et al. 1991a, 1992, 1993, 1995; Köhrle 1994). Selenium supplementation of individuals deficient in both iodine and selenium produces a further decrease in thyroid function, but if selenium supplementation is preceded by normalization of iodine levels, then normal thyroid function is restored (Contempré et al. 1991, 1992). Selenium supplementation also affects thyroid hormone levels in humans with no iodine deficiency; these effects include decreases in serum T_3 and T_4 levels and increases in serum TSH levels, suggesting suppression of thyroid hormone production (Brätter and Negretti De Brätter 1996; Duffield et al. 1999; Hagmar et al. 1998; Hawkes and Turek 2001). The necrotizing effect of iodine on thyroid cells was greater in selenium-deficient rats than in selenium-supplemented rats (Contempré et al. 1993). Other studies in rats showed that selenium deficiency causes decreased metabolic clearance of iodothyronines and decreased extrathyroidal production of T_3 , as a result of decreased iodothyronine deiodinase activity, which can be restored to normal by selenium repletion (Arthur and Beckett 1989, 1994; Behne and Kyriakopoulos 1993). The effects observed in iodine and selenium deficient humans and animals is consistent with a proposed mechanism in which (1) iodine deficiency results in hyperstimulation of the thyroid by TSH and consequently in increased production of H_2O_2 within the cells, (2) selenium deficiency results in GPX deficit and consequently in accumulation of H_2O_2 , and (3) induction of thyroid cell necrosis and fibrosis from the excess H_2O_2 that cannot be detoxified due the lack of GPX (Contempré et al. 1995; Delange 2000; Köhrle 1994). The available data suggest that iodine supplements could cause adverse effects in selenium-deficient individuals.

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Mercury. Simultaneous administration of mercury and selenium in equimolar doses to animals resulted in decreased toxicity of both elements in acute and chronic studies with inorganic and organic mercury and with either inorganic or organic selenium compounds, although inorganic forms of selenium appear to be more effective than organic forms (Chang 1983; Rao et al. 1998; Skerfving 1978). Selenium protects against the acute nephrotoxicity of the mercuric ion and methylmercuric ion in rats (Ganter et al. 1972; Hansen 1988; Magos et al. 1987; Parizek and Ostadalova 1967) and possibly against acute neurotoxicity of the methylmercuric ion in rats (Ohi et al. 1980). The protective effect of selenium has been associated with a higher whole body retention of mercury rather than with increased mercury excretion (Hansen 1988; Magos et al. 1987). Selenium has been shown to inhibit biliary excretion of methyl mercury in rats (Urano et al. 1997), while mercury exposure reduces urinary selenium excretion in humans (Ellingsen et al. 1995). Although the mechanism of the interaction has not yet been elucidated, selenium and mercury appear to form a metabolically inert compound by reaction with GSH (Gailer et al. 2000b). Further support for the role of this compound comes from the observation that selenium-treated animals can remain unaffected despite an accumulation of mercury in tissues to levels that are otherwise associated with toxicity (Skerfving 1978). Additional support comes from the 1:1 ratio of selenium and mercury found in the livers of marine mammals and in the bodies of experimental animals injected with mercury and selenium, regardless of the ratio of the administered doses (Hansen 1988).

Although the fetotoxicity of methylmercuric chloride has been enhanced in selenium-deficient mice (Nishikido et al. 1987), additional selenium administration does not appear to protect against teratogenic effects (i.e., cleft palate) of methylmercuric chloride in mice (Lee et al. 1979). High doses of selenium administered as selenite for 30 days prior to gestation and through gestation day 18 to mice fed a diet containing high doses of methylmercuric chloride increased the incidence of cleft palate (Nobunaga et al. 1979). Concurrent treatment of pregnant or lactating mice receiving nontoxic doses of methyl mercury in drinking water with selenomethionine increased the deposition of mercury in the offspring (Nielsen and Andersen 1995).

Methionine and Vitamin E. Combinations of methionine and vitamin E have been found to be antagonistic to selenium toxicity. In one study, selenium concentrations in the liver and kidneys of rats fed selenium (sodium selenate)-containing diets with methionine and vitamin E were less than the concentrations found in the livers and kidneys of rats fed selenium with either methionine or vitamin E alone (Levander and Morris 1970). The results are compatible with the hypothesis that methionine detoxifies selenium by forming methylated derivatives of selenium that are eliminated in the urine and in

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expired air (see Section 3.4.4) (Stadtman 1977, 1980, 1983, 1987, 1990). As discussed in Section 3.11, methionine administered as an antidote for acute selenium toxicity in rats was ineffective (Lombeck et al. 1987).

Silver. Selenium has been shown to be protective against the hepatotoxic effects of silver in vitamin E-deficient rats. A 0.15% solution of silver acetate in the drinking water of rats produced necrotic degeneration of the liver and high mortality. Dietary selenium supplementation at 1 mg selenium/kg food resulted in a significant reduction in the toxic effects of silver (Diplock et al. 1967). One report indicates a nontoxic dose of silver acetate in rats minimizes effects of acute selenium toxicity. However, the body burden of selenium in several organs increased with treatment with silver acetate. It is postulated that this antagonistic effect may be due to the formation and disposition of silver selenides, which are relatively insoluble and nontoxic (Eybl et al. 1992).

Sulfate. Sulfate appears to reduce the growth inhibition that results from dietary exposure of rats to high levels of selenite or selenate (Halverson and Monty 1960). Sulfate does not appear to be protective against selenium-induced liver damage (Halverson and Monty 1960).

Antagonistic interactions with several additional metals including antimony, germanium, and bismuth have been reported (Paul et al. 1989). Complex interactions of selenium with other metals, vitamins, and nutrients usually lead to a reduced toxicity of selenium and/or a reduced toxicity of the interacting substance. However, vitamin C (ascorbic acid) may increase the absorption and toxic effects of selenium in humans (HSDB 2001; Lombeck et al. 1987; Mack 1990; Martin et al. 1989a, 1989b). The relevance of these interactions to selenium exposure of the general public is unknown. Many review articles are available concerning the interactions of selenium and other chemicals, including those by Combs, Jr., and Combs (1987), Hansen (1988), Levander (1972), Magos and Webb (1980), Naganuma et al. (1983), and Whanger (1981).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to selenium than will most persons exposed to the same level of selenium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of selenium, or compromised function of organs

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affected by selenium. Populations who are at greater risk due to their unusually high exposure to selenium are discussed in Section 6.7, Populations With Potentially High Exposures.

Data concerning human subpopulations with unusual susceptibility to the toxic effects of selenium were not located. Epidemiologic studies have identified populations with very low or very high nutritional status, and these groups are expected to have very different responses to selenium exposures. Pregnant and nursing women are believed to require more selenium than the general public (NRC 1989).

It is possible that persons exposed to high fluoride levels in drinking water might be at greater risk of adverse health effects from exposure to excessive levels of selenium (Moxon and DuBois 1939; Yang et al. 1989a), but evidence on this point is equivocal (Hadjimarkos 1969a) and requires further study. Individuals with vitamin E-deficient diets might also be at greater risk of liver damage from exposure to excess selenium (Levander and Morris 1970). Based on studies of chemically induced diabetes in rats, selenium may change insulin needs (McNeil et al. 1991). Therefore, insulin-dependent diabetics may be more sensitive to adverse health effects due to selenium exposure than the general population.

Cretins or other individuals with iodine or thyroid deficiencies may be more sensitive to adverse health effects from selenium exposure (Contempré et al. 1991b, 1992). Iodine supplementation of these individuals without selenium supplementation may further exacerbate the effects. The elderly may be less susceptible to the negative effects of selenium and more prone to selenium deficiencies. A number of researchers have reported lower absorption of selenium and lower selenium tissue concentrations in the elderly compared to younger adults (Martin et al. 1991; Morisi et al. 1989).

Populations living in the western United States in areas eating produce grown in highly seleniferous soils could be at greater risk of adverse health effects from additional environmental exposure to selenium if their selenium nutritional status is already high (see Section 6.6).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to selenium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to selenium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted

for medical advice. The following texts provide specific information about treatment following exposures to selenium:

Nadig RJ. 1994. Cadmium and other metals and metalloids. In: Goldfrank LR, Weisman RS, Flomenbaum N, et al. eds. Goldfrank's toxicological emergencies. 6th ed. Norwalk, CT: Appleton and Lange, 1342-1343.

Mofenson HC, and Caraccio TR. 1998. Toxicity of household products. In: Viccellio P, ed. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven, 519.

3.11.1 Reducing Peak Absorption Following Exposure

No specific recommendations have been reported for reducing absorption following acute high-dose exposure to selenium or selenium compounds via inhalation or dermal exposure (Gosselin et al. 1984; HSDB 2001). There have been very few reported cases of overexposure via inhalation in industrial settings but some have resulted in toxic effects (Lockitch 1989). General procedures suggested for reducing absorption following accidental industrial exposure include moving the exposed person into fresh air, removing contaminated clothing and shoes, and flushing exposed skin or eyes with running water (HSDB 2001).

Oral exposures to toxic quantities of selenious acid, sodium selenate, and selenium dioxide have been reported (Lockitch 1989). In general, only supportive treatment has been recommended (HSDB 2001; Mack 1990). In some cases, gastric lavage and induction of vomiting by use of emetics have been reported to be useful in reducing absorption, but because selenious acid (in gun bluing, pH 1) is caustic, both procedures could result in additional damage by this compound (Lombeck et al. 1987; Mack 1990). The possibility of a sudden onset of shock, seizures, severe hypotension, and cardiorespiratory arrest has been used to argue against emesis (Mack 1990). It has also been suggested that oils and alcohol are to be avoided in treatment of ingested selenium sulfide because these agents may increase absorption (Gosselin et al. 1984).

3.11.2 Reducing Body Burden

In acute exposure situations, selenium compounds are rapidly absorbed and widely distributed throughout many organ systems following inhalation or ingestion (see Section 3.4.2). Extensive parenteral fluid administration has been used to force the urinary excretion of selenium (Lombeck et al. 1987). Chelating

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agents have not been effective in experiments, and both calcium disodium ethylene diamine tetraacetate (EDTA) and dimercaprol (British Anti-Lewisite, BAL) may increase the toxic effects of selenium (Lombeck et al. 1987; Mack 1990; Paul et al. 1989). Although vitamin C (ascorbic acid) is used to reduce the body burdens of other metals, it may also increase the absorption and toxic effects of selenium in humans (HSDB 2001; Lombeck et al. 1987; Mack 1990; Martin et al. 1989a, 1989b). Bromobenzene has been reported to increase the urinary excretion of selenium, but because bromobenzene is also a hepatic toxin, its use is dangerous (Gosselin et al. 1984; HSDB 2001).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The exact molecular mechanism of toxic action by selenium and selenium compounds is not known. One theory is that at a biochemical level, selenium inactivates sulfhydryl enzymes leading to depression of cellular oxidative processes (Lombeck et al. 1987; Mack 1990; Shamberger 1981). No information was located on established therapies designed to interfere with this possible mechanism of action of selenium. Because selenomethionine is known to randomly insert into proteins, rats were treated with methionine after acute selenosis had developed, but no effect was observed (Lombeck et al. 1987). However, pretreating rats with dietary methionine and vitamin E reduced the toxicity of dietary selenium as measured by decreased liver damage, reduced body weight gain, and decreased liver and kidney concentrations of selenium compared to those in rats that had not received supplements (Levander and Morris 1970). Inorganic sulfate fed simultaneously with selenite or selenate in the diet protected rats from the toxicity of selenium as measured by body weight gain; however, sulfate did not protect against liver necrosis caused by selenium (Halverson et al. 1962). It would, therefore, seem plausible that another nontoxic sulfur-containing chemical could be found to be effective against acute selenium toxicity.

The search for an agent that both reduces the acute toxicity of selenium and increases the excretion of the selenium compound formed has proved difficult (Paul et al. 1989). In some experimental cases, other metals have been shown to mitigate the toxicity of selenium, possibly by forming metal selenides with low solubility and toxicity (see Section 3.9). Several metal-containing compounds were tested for efficacy in reducing toxic effects and increasing elimination of selenium from sodium selenate injected into rats. Germanium citrate is nontoxic and was found to be effective both at reducing toxic effects and increasing the rate of selenium elimination. However, the germanium compound, bis-carboxyethyl germanium sesquioxide, had no positive effect on toxicity or distribution to organs but did increase the amount of selenium excreted in the urine (Paul et al. 1989). In mice, pretreatment with a nontoxic dose of

silver acetate was shown to reduce the toxic effects of sodium selenite. However, this treatment increased the whole body burden of selenium, and the concentrations in several organs were raised compared to those in the controls injected with sodium selenite only (Eybl et al. 1992). Arsenic was proposed as a possible prophylactic against selenium poisoning in workers, based on counteraction of selenium toxicity in pigs exposed to sodium arsenate (Amor and Pringle 1945).

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of selenium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of selenium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Selenium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to selenium are summarized in Figure 3-10. The purpose of this figure is to illustrate the existing information concerning the health effects of selenium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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Figure 3-10. Existing Information on Health Effects of Selenium

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●				●				●
Oral	●	●		●	●	●	●			●
Dermal		●								

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●								
Oral	●	●	●	●	●	●	●	●	●	●
Dermal					●					●

Animal

● Existing Studies

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As seen in Figure 3-10, very little quantitative information is available regarding the health effects in humans exposed to selenium compounds via inhalation. The only quantitative inhalation studies in humans that relate selenium exposure levels or selenium body levels to health effects following inhalation exposure are epidemiological cancer studies. Fatalities following inhalation exposure to selenium compounds have not been reported. Despite the large number of cases of reported inhalation exposures in occupational settings, characterization of exposure concentrations and the selenium compounds present in the air are generally lacking. It is therefore not possible to link the degree and types of symptoms reported in workers to selenium exposure levels. There have been no reports of immunological, developmental, reproductive, or genetic effects in humans resulting from inhalation exposure to selenium compounds. Complaints of dizziness and fatigue have accompanied occupational inhalation exposures, but characterization of the exposure levels required to produce neurological symptoms is lacking.

Most of the information concerning the health effects in humans following exposure to selenium and selenium compounds is for the oral exposure route. However, exposure levels associated with the few documented fatalities resulting from accidental or suicidal poisoning with selenium compounds are lacking, as are exposure levels for other nonfatal poisonings by ingestion. A series of epidemiological studies in China have provided the only data about chronic exposure levels to excess dietary selenium that resulted in adverse effects on skin, nails, and hair and in possible neurological effects.

Older reports from the western United States described similar symptomology in the 1930s, but did not characterize daily selenium intake. More recent reports show no clinical symptoms in the same area. The possible inverse relationship between dietary selenium intake and the risk of various types of cancer has been examined in numerous epidemiological studies in the United States and other countries.

Concern for the dermal route of exposure to selenium compounds as a cause of adverse health effects in humans is extremely low except for the acid forms, which owe their dermal effects to their acidity more than to their selenium content. Selenium sulfide, an ingredient in some antidandruff shampoos, does not appear to be absorbed through the skin. Ingestion of large amounts of the compound, however, would be of concern because selenium sulfide has been shown to be carcinogenic in rats and mice following oral exposure.

Data are available for acute inhalation exposures for a few of the volatile selenium compounds that have resulted in the death of animals. These exposures also produced signs of central nervous system toxicity,

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lung injury, and possible damage to heart and liver. No studies were located concerning health effects in animals following intermediate or chronic inhalation exposures to volatile selenium compounds or selenium dust.

In animals, the focus on the oral toxicity of selenium has taken two routes, one in laboratory animals and the other in studies of selenium toxicity to livestock. In laboratory animals, attention has been directed toward the hepatotoxic properties of selenites, selenates, and selenium contained in grains following early reports that selenium produced hepatic carcinomas in rats. An intermediate-duration study has also shown that selenate and selenite can cause kidney effects in rats while mice are less sensitive to this effect of selenium compounds. In recent years, much of the research in laboratory animals using the oral route of administration of selenium compounds has been directed toward the anticarcinogenic properties of selenium compounds.

In livestock, concern for selenium toxicity and deficiency is high. In areas of the country with selenium-poor soils, dietary selenium supplementation for livestock has been necessary to prevent chronic selenium deficiency diseases. Dietary supplementation programs have resulted in cases of accidental poisonings from misuse of the selenium supplements (Hopper et al. 1985).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The primary target organ in humans following acute exposure to high concentrations of selenium by inhalation or oral routes is the lung, with cardiovascular, hepatic, and renal systems all affected (lesser systemic effects were observed in all other organ systems except the musculoskeletal system) (Carter 1966; Civil and McDonald 1978; Clinton 1947; Koppel et al. 1986; Wilson 1962). Two case reports of acute dermal exposure were also located; the results revealed effects on the skin and eyes (Middleton 1947; Pringle 1942). Additional epidemiological or occupational studies would be useful to further characterize the effects of acute exposure via all routes and to confirm the target organ data.

Studies regarding single inhalation or oral exposures of rats, guinea pigs, rabbits, and mice have provided information on lethal levels of exposure to selenium compounds (Cummins and Kimura 1971; Dudley and Miller 1941; Hall et al. 1951; Miller and Williams 1940; Olson 1986; Smyth et al. 1990). However, few levels at which sublethal effects first appear have been identified. Clinical observations and gross

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necropsies have been performed, but no single-dose exposure study has included internal examination of the animals to identify dose-response data for sublethal systemic toxic effects. Such studies might provide information on the thresholds for systemic toxicity following single-dose exposure. Repeated inhalation exposure studies in animals are limited to a few days of exposure (Hall et al. 1951). Although the studies have demonstrated cumulative toxicity following repeated inhalation exposure to inorganic selenium compounds, effects other than lethality have been poorly characterized. Single-dose exposure studies have been conducted with selenium monosulfide in mice (target systems: respiratory and neurological) and selenium disulfide in rats (target organ not specified); however, the results have varied and there is uncertainty about which or how much of each of the compounds was administered. There were no effects in mice following acute dermal exposure. Additional dermal exposure studies in animals would be useful to confirm the effects found in humans. The data were insufficient for the derivation of acute oral and inhalation MRLs.

Intermediate-Duration Exposure. No human studies of intermediate inhalation exposure to selenium were located. Following oral exposure, one study in humans revealed endocrine effects in iodine-deficient individuals (Contempré et al. 1991a, 1992) and others revealed endocrine effects in individuals receiving sufficient levels of iodine (Duffield et al. 1999; Hawkes and Turek 2001). Results from one study in humans revealed dermal effects following intermediate dermal exposure (Pringle 1942). There were insufficient data to derive intermediate MRLs. Additional epidemiological or occupational studies would be useful in elucidating the potential target organs and effect levels.

No intermediate inhalation studies were located in animals. Intermediate-duration inhalation studies, in which selenium is administered as selenium dioxide, hydrogen selenide, or selenium dust, might help to identify air concentrations of these substances that produce sublethal effects not only on the respiratory system, but also on the hepatic, renal, hematological, and cardiovascular systems. As exposure to the selenoamino acids is via ingestion, inhalation studies of these compounds would not be necessary.

Intermediate-duration oral exposure studies have been performed with rats, pigs, mice, and monkeys at several dose levels using several selenium compounds (Baker et al. 1989; Behne et al. 1992; Bioulac-Sage et al. 1992; Chen et al. 1993; Cukierski et al. 1989; Das et al. 1989b; Eder et al. 1995; Halverson et al. 1966; Hasgawa et al. 1994; Hotz et al. 1997; Mahan and Magee 1991; Mihailovic et al. 1992; NTP 1980c, 1994; Palmer and Olson 1974; Panter et al. 1996). The major effects were hepatic, dermal, endocrine, and neurological. Additional studies are needed to confirm these data. No intermediate-duration dermal administration studies have been conducted with the environmental forms of inorganic

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selenium likely to be of concern (e.g., sodium selenate and sodium selenite), although it is unlikely that these forms would be dermally absorbed to a significant degree. Dermal application of selenomethionine to the skin of mice did not result in any direct effects on the skin, or other signs of toxicity, although it was absorbed (Burke et al. 1992b). The organic compounds of selenium are usually not free in the environment but, rather, are contained in plant and animal material. Therefore, no further dermal studies would be useful.

Chronic-Duration Exposure and Cancer. Several occupational studies of chronic inhalation exposure to inorganic selenium compounds were located (Glover 1967; Holness et al. 1989; Kinnigkeit 1962). Effects reported in these studies were primarily respiratory, although cardiovascular, gastro-intestinal, hematological, musculoskeletal, dermal, ocular, and neurological effects were also noted. Animal data are not available for inhalation exposures of chronic duration. Data in this area would be helpful to establish an animal model for respiratory effects of inorganic selenium compounds, since most human exposure has been occupational and to a variety of compounds. Neurological effects have been documented in animals after chronic oral exposure, but further study of neurological effects in animals after inhalation exposure is needed to provide a model for the effects observed after occupational exposure in humans. Following chronic oral exposure, the primary effects in humans were dermal, neurological, and endocrine (Brätter and Negretti De Brätter 1996; Clausen et al. 1989; Longnecker et al. 1991; Yang et al. 1983, 1989a, 1989b; Yang and Zhou 1994). An MRL has been derived for chronic oral exposure to selenium based on a NOAEL for dermal effects. One case report of chronic dermal exposure revealed dermal effects (Senff et al. 1988). Additional epidemiological or retrospective studies of chronic exposure would be helpful for confirming the existing data. Studies examining the role of nutrition in selenium toxicity would be especially useful.

Although the lung does not appear to be a target organ in animals after chronic oral exposure to selenium compounds, data have not been adequately reported (Harr et al. 1967; Henschler and Kerschner 1969; Schroeder and Mitchener 1972), and further studies might be useful to fully rule out these effects. Studies examining possible gastrointestinal and musculoskeletal effects in animals after chronic exposure to selenium or selenium compounds or to seleniferous grains might be helpful in determining the mechanisms of alkali disease whose symptoms have been observed in grazing livestock (Harr et al. 1967; Shamberger 1986). Hepatic and renal lesions following chronic selenium exposure have been adequately characterized. Investigations of systemic effects associated with chronic oral administration of selenium compounds, however, have been limited.

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No studies were located regarding carcinogenic effects in animals after chronic inhalation exposure to selenium or selenium compounds. No further investigation is needed since humans have not been shown to have an increased risk of malignancy from selenium exposure. The majority of oral studies have provided information on the absence of carcinogenic effects in humans and animals (Beems 1986; Clark et al. 1996a, 1999; Coates et al. 1988; Duffield-Lillico et al. 2002; Harr et al. 1967; Menkes et al. 1986; Reid et al. 2002; Thompson and Becci 1979; Virtamo et al. 1987). However, earlier and less complete studies had suggested that selenium was carcinogenic following oral exposure of animals (Nelson et al. 1943; Schroeder and Mitchener 1971a; Volgarev and Tscherkes 1967). Chronic oral exposure studies conducted in mice and rats by gavage administration of a mixture of selenium monosulfide and selenium disulfide produced liver tumors in rats and lung tumors in female mice (NTP 1980c). The relative proportion of the two compounds was not clear, although physical evidence suggested that the dose solution was primarily selenium monosulfide. Further studies utilizing selenium sulfides might be useful in determining possible effects in humans.

Genotoxicity. Chromosomal aberrations and sister chromatid exchanges in lymphocytes were not increased in humans treated (oral or intramuscular injection) with sodium selenite (Norppa et al. 1980a). Compared to untreated controls, a significant increase in the number of micronuclei was observed in bone marrow cells of mice treated orally with selenite or selenate, and macaques treated orally with L-selenomethionine (Biswas et al. 1997, 1999a; Choy et al. 1989; Itoh and Shimada 1996; Rusov et al. 1996). A significant increase in the number of micronuclei in bone marrow cells was not observed in the offspring of macaques treated with L-selenomethionine on gestation days 20–50 (Choy et al. 1993).

Genotoxicity studies (*Salmonella*/microsome assays, sister chromatid exchange, and tests of unscheduled DNA synthesis and of chromosome aberrations in cultured mammalian cells) indicate that selenite, selenate, and selenide have both genotoxic and antigenotoxic effects (Biswas et al. 1997, 2000; Gairola and Chow 1982; Khalil 1994; Lu et al. 1995b; Schillaci et al. 1982; Ueda et al. 1997; van der Lelie et al. 1997). The underlying mechanisms responsible for the varying genotoxicity results remain to be elucidated.

Reproductive Toxicity. One study that measured the concentration of selenium in sperm samples indicated no correlation between selenium concentrations and sperm count or motility (Roy et al. 1990). No significant increase in spontaneous abortions was reported among women chronically exposed to drinking water containing 7–9 µg/L selenium (Vinceti et al. 2000a). This study is limited by a level of selenium in water that is not generally considered to be high, lack of data on selenium status, and

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insufficient information on confounding variables. No other human studies were located. A few reproductive toxicity studies in animals (Chowdhury and Venkatakrishna-Bhatt 1983; Harr and Muth 1972; NTP 1996; Schroeder and Mitchener 1971b; Wahlstrom and Olson 1959b) indicate that oral exposure to excess sodium selenite can reduce female fertility, although male fertility appears not to be affected. Oral treatment of rats with sodium selenate or selenite has been shown to increase the number of abnormal sperm in males (El-Zarkouny et al. 1999; Kaur and Parshad 1994; NTP 1994), produce testicular hypertrophy (Turan et al. 1999a), and affect the estrous cycle (NTP 1994, 1996). Fertility was not examined in these studies. Selenium dioxide produced testicular degeneration following intraperitoneal administration to rats (Chowdhury and Venkatakrishna-Bhatt 1983). Disturbances in the menstrual cycle (anovulation, short luteal and follicular phases) were observed in monkeys treated orally with L-selenomethionine (Cukierski et al. 1989) and mice treated orally with sodium selenite (Nobunaga et al. 1979). Studies of both male and female reproductive toxicity of selenium following oral and inhalation exposure in rats and other mammals to selenium dioxide and other forms of selenium, both organic and inorganic, would be useful. Such studies could provide information regarding the reproductive effects of the various forms of selenium that might be encountered in occupational settings, at waste sites, and in the drinking water and food from highly seleniferous areas of the United States.

Developmental Toxicity. No developmental studies were found regarding inhalation or dermal exposure in humans or animals. Developmental studies using the oral route of administration indicate that excessive sodium selenate or sodium selenite intake can result in fetal toxicity and reduced growth in experimental mammals (Dinkel et al. 1963; Ferm et al. 1990; NTP 1996; Rosenfeld and Beath 1964; Wahlstrom and Olson 1959a), but generally only at doses that produce maternal toxicity. Developmental effects were not observed in macaque fetuses from mothers given toxic oral doses of L-selenomethionine during gestation (Tarantal et al. 1991). Intravenous injection of sodium selenite in mice did not indicate that the compound is teratogenic in rodents (Yonemoto et al. 1984). Intravenous injections of sodium selenate, D,L-selenomethionine, and D,L-selenocystine into neonatal rats indicated that some selenium compounds can contribute to the formation of one type of cataracts (Ostadalova and Babicky 1980). Cataracts were not observed in the offspring of macaques treated orally with L-selenomethionine during gestation (Tarantal et al. 1991). Additional developmental toxicity studies of selenium compounds in mammals do not seem to be necessary at this time.

Immunotoxicity. No studies were located regarding adverse immunological effects in humans following inhalation or oral exposure. One case report describes immunological effects following dermal exposure (Senff et al. 1988). Animal studies of possible adverse immunological effects from excessive

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exposure to selenium compounds are limited (Dudley and Miller 1941; Glenn et al. 1964a; Hall et al. 1951; Smyth et al. 1990). One study (Koller et al. 1986) included a battery of immunological tests, some of which indicated beneficial effects of sodium selenite administration and others that indicated adverse effects. Additional immunotoxicity tests, including challenges of the immune system, might characterize the significance of the different immunological effects that have been observed following selenium administration.

Other than selenium sulfide, an ingredient in some antidandruff shampoos, selenium compounds have not been tested for sensitization. The potential for dermal contact by humans does exist, however, in occupational settings and to a lesser extent in soil at waste sites.

Neurotoxicity. Data from an epidemiological study of humans and from studies in livestock indicate that the central nervous system is an end point of concern following oral exposure to selenium compounds (Baker et al. 1989; Boylan et al. 1990; Cukierski et al. 1989; Harrison et al. 1983; Panter et al. 1996; Rosenfeld and Beath 1964; Stowe et al. 1992; Tsunoda et al. 2000; Yang et al. 1983). Chronic oral exposure studies of laboratory animals that focus on behavioral effects and histopathological changes in the central nervous system might provide useful dose-response information on central nervous system effects.

Epidemiological and Human Dosimetry Studies. A few human epidemiological studies have identified blood selenium levels indicative of adequate selenium status and indicative of selenium toxicity. However, there are large differences in selenium blood levels in populations from different parts of the world (e.g., China, New Zealand, and Finland) (Salonen et al. 1985; Yang et al. 1989a). For example, blood selenium levels in healthy New Zealand populations averaged 0.059 mg selenium/L (Rea et al. 1979), whereas blood selenium levels in healthy U.S. populations were much higher, averaging 0.206 mg selenium/L (Allaway et al. 1968). Extrapolation from the relationship between blood selenium levels and selenium toxicity in populations from one region of the world to populations in another region may not be appropriate. Studies examining the particular forms of selenium and the contribution of diet in determining individual and population selenium status would be useful. The selenium status of an individual will determine the magnitude of additional selenium intake that can be tolerated without resulting in adverse effects. Evidence for adverse effects on the endocrine system has also been found following intermediate and chronic oral exposure to elevated levels of dietary selenium in humans and animals (Brätter and Negretti De Brätter 1996; Behne et al. 1992; Eder et al. 1995; Hawkes and Turek 2001; Hotz et al. 1997). Studies of humans with high dietary intakes of selenium that monitored thyroid

hormone levels and iodine intake would be useful. Studies of humans taking selenium supplements would also help further identify the long-term effects of selenium status on human health.

Biomarkers of Exposure and Effect.

Exposure. Selenium exposure can be correlated with concentrations detected in human blood, blood components, urine, hair, and nails. Selenium concentrations found in these biomarkers in the general population can be found in Table 3-7. However, these markers vary greatly among different populations (Longnecker et al. 1991). Levels of plasma, erythrocyte and platelet GPX activity, as well as selenoprotein P may serve as better markers of selenium deficiency than selenium concentrations. Additional research into markers of selenium status in populations and how they may be used to estimate an additional selenium exposure that would be safe would be helpful.

Effect. There currently are no good preclinical indicators of selenium toxicity. Perhaps the earliest and most frequent symptoms of selenosis in humans are dry and brittle hair that breaks off, and brittle nails with white spots or streaks. Although these effects may not be specific to selenium, determination of selenium status could be useful if they are observed in a subject. Additional biomarkers of negative effects that could be detected before clinical signs of selenium toxicity would be helpful in identifying and preventing selenium poisoning.

Absorption, Distribution, Metabolism, and Excretion. The absorption of selenium has been investigated in humans following oral exposure and in animals following oral and inhalation exposures (Finley 1998; Glover 1970; Griffiths et al. 1976; Martin et al. 1989a; Medinsky et al. 1981a; Sánchez-Ocampo et al. 1996; Thomson et al. 1977). In humans, no quantitative data exist on either the extent or rate of absorption of selenium from the lung or the skin. Information that selenium is absorbed following inhalation is limited to occupational case studies in which larger quantities of selenium have been measured in the urine of workers occupationally exposed to selenium. In order to understand all possible routes for human overexposure to selenium, information concerning the dermal and inhalation absorption of selenium and its compounds in humans would be useful, even though potential exposures to selenium might be more likely to occur by the oral route for the general public.

The oral absorption of different physical and chemical forms of selenium (e.g., selenite, selenate, and selenomethionine as solids or in aqueous solution) has been investigated in humans (Griffiths et al. 1976; Martin et al. 1989a; Moser-Veillon et al. 1992; Robinson et al. 1978; Swanson et al. 1991; Thomson

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1974; Thomson and Stewart 1974; Thomson et al. 1977) and in animals (Finley 1998; Furchner et al. 1975; Thomson and Stewart 1973; Vendeland et al. 1992; Whanger et al. 1976). Oral absorption of naturally occurring selenium and the effects of dietary levels on the absorption of exogenous selenium have also been investigated (Young et al. 1982). These studies have revealed that several selenium compounds appear to be readily absorbed from the gastrointestinal tract of humans and animals. It also appears that the degree of absorption in humans is independent of the exposure level, but that in some cases, absorption is greater when a selenium deficiency exists.

Distribution studies in humans and animals indicate that selenium is widely distributed in the body and is concentrated in the liver and kidney following oral, intravenous, or subcutaneous exposures (Cavalieri et al. 1966; Finley 1998; Heinrich and Kelsey 1955; Jereb et al. 1975; Kaneko et al. 1999; Mahan and Kim 1996; Razagui and Haswell 1997; Shiobara et al. 1998; Thomson and Stewart 1973). Studies of intravenous administration of selenomethionine have indicated that animals and humans concentrate this compound in the pancreas, but it is unlikely that this selenium compound will be encountered in large quantities in the environment except in animals and plants along with other organic selenium compounds. It would be useful to know if selenomethionine concentrates in the pancreas of humans following oral intake. Following oral exposure, the distribution of selenium across the placenta into the fetuses of rats, hamsters, dogs, and monkeys (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Mahan and Kim 1996; Parizek et al. 1971a; Willhite et al. 1990) and the transfer of selenium from milk to suckling offspring of rats, dogs, and monkeys (Archimbaud et al. 1992; Choy et al. 1993; Hawkes et al. 1994; Parizek et al. 1971a) have also been investigated. Selenium levels have been measured in human milk (Brätter and Negretti De Brätter 1996; Brätter et al. 1991b; Li et al. 1999; Michalke and Schramel 1998; Moser-Veillon et al. 1992; Rodríguez Rodríguez et al. 1999; Viitak et al. 1995; Yang 1989b), and the concentration of selenium in human milk has been shown to correlate with dietary intake (Brätter et al. 1991b). The uptake of selenium by erythrocytes and its subsequent metabolic alteration and ultimate binding to plasma proteins have been investigated (Sandholm 1973).

The metabolism of selenium is now fairly well understood. To become incorporated into selenium-specific proteins (e.g., glutathione peroxidase, thioredoxin reductase, iodothyronine 5'-deiodinase) through a cotranslational mechanism requires that selenium be in the form of selenide (Sunde 1990). All forms of selenium can be transformed to selenide, although the rates of transformation vary. For example, selenate is not converted to selenide as readily as selenite. The formation of selenide from selenocysteine requires a specific enzyme, selenocysteine β -lyase, which catalyzes the decomposition of selenocysteine to alanine and hydrogen selenide. Excess selenium can be methylated and exhaled or

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excreted in the urine in both humans and animals. Further research is required to determine which selenium metabolites or intermediates lead to toxicity.

In humans and animals, intravenous and oral administration data indicate that the major route of selenium excretion is in the urine (Byard and Baumann 1967; Davidson-York et al. 1999; Finley 1998; Griffiths et al. 1976; Palmer et al. 1970; Patterson et al. 1989; Shiobara et al. 1998; Swanson et al. 1991). Excretion of selenium in feces constitutes a minor pathway immediately following exposure, but the amount excreted can be equal to that excreted in urine depending on the chemical form of selenium administered, the size of the dose, and the length of time since dosing. Both human and animal studies indicate that the extent of excretion by any one route is related to the administered dose and the frequency of administration (Finley 1998; Lathrop et al. 1972; McConnell and Roth 1966; Shiobara et al. 1998; Thomson and Stewart 1974). The extent of excretion of selenium compounds in the expired air has been investigated in animals, but no quantitative studies in humans for this route exist; however, it is believed to be a minor pathway especially at lower doses (McConnell and Roth 1966; Olson et al. 1963).

Comparative Toxicokinetics. The target organs and adverse health effects are generally similar across species. However, the liver appears to be the primary target organ for the oral toxicity of selenium in animals following intermediate and chronic exposure (Baker et al. 1989; Biolac-Sage et al. 1992; Fitzhugh et al. 1944; Halverson et al. 1970; Harr et al. 1967; Hasegawa et al. 1994; Kolodziejczyk et al. 2000; Nelson et al. 1943; Palmer and Olson 1974; Sayato et al. 1993; Schroeder and Mitchener 1972; Skowerski et al. 1997a; Turan et al. 1999a), whereas liver cirrhosis or dysfunction have not been found in reports of chronic selenosis in humans (Longnecker et al. 1991; Yang et al. 1989a). Different metabolites may help explain the cataract formation observed in neonatal rats and the teratogenic activity of selenium seen in birds but not in humans or other mammals (Tarantal et al. 1991). Toxicokinetic studies with some design similarities have been performed in humans and several animal species (Behne et al. 1991; Bopp et al. 1982; Cantor et al. 1975; Ganther 1979; Hawkes et al. 1992; Obermeyer et al. 1971; Palmer et al. 1970; Willhite et al. 1990, 1992). Comparative toxicokinetic studies, per se, have not been performed. PBPK models for selenium administered orally as selenite or selenomethionine have been developed for humans, but no animal models were located. Animal models for the oral route would be useful in assessing toxicokinetic similarities and differences between species.

Methods for Reducing Toxic Effects. Current methods for reducing toxic effects of selenium and selenium compounds after acute exposures are general supportive treatment methods based on those used for other toxic metals (HSDB 2001; Mack 1990). Because there is no suitable way to treat either acute or

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chronic selenium poisoning, additional research aimed at decreasing absorption, speeding excretion, and reducing the body burden of selenium would be valuable.

Children's Susceptibility. Limited information is available on the toxicity of selenium in children, but the available information suggests that children may be less susceptible to toxic effects of selenium than adults and more susceptible to deficiency. Most data comes from children living in areas of chronic high dietary selenium intake (Yang et al. 1989a, 1989b). Additional research on age specific effects of selenium toxicity does not appear necessary at present.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The American Health Foundation is involved in on-going research to develop new organoselenium chemopreventive agents for cancer having an increased therapeutic ratio compared with some of the historical selenium compounds, such as selenite. Additional federally sponsored research that was reported in the CRIS/USDA (2002), CRISP (2002), and FEDRIP (2002) databases is shown in Table 3-8.

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Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
Alberts, DS	University of Arizona	Phase III trials of chemopreventive agents on colon carcinogenesis	CRISP 2001
Aposhian, HV	Not Available	Detoxification of metals – <i>In vitro</i> and <i>in vivo</i> studies	CRISP 2002
Bar-Noy, S and Nhlbi, NIH	National Institutes of Health	Mammalian thioredoxin reductase	FEDRIP 2002
Beck, MA	University of North Carolina	The influence of nutrition on influenza virus infection	FEDRIP 2002
Bell, J	Not available	Effects of selected metal salts on the fidelity of DNA synthesis <i>in vitro</i>	CRISP 2002
Bennish, ML	National Institutes of Health	Micronutrients and enteric infection in African children	FEDRIP 2002
Beran, M	Vyzkumny Ustav Potravinarsky	Evaluation of combined supplementation with selenium and iodine on levels of selenium-dependent enzymes, thyroidal hormones and other biochemical parameters	CRIS/UDSA 2001
Berry, MJ	Brigham and Women's Hospital	Mechanism of selenoprotein synthesis in eukaryotes	CRISP 2001
Berry, MJ	Brigham and Women's Hospital	Selenoprotein P function and regulation of expression	CRISP 2002
Block, E	Roswell Park Memorial Institute	Identify selenium compounds from high-selenium garlic	CRISP 2001
Bosland, MC	New York University School of Medicine	Preclinical prostate cancer chemoprevention studies	CRISP 2001
Burk, RF	Vanderbilt University	Nutritional and metabolic significance of selenium	FEDRIP 2002
Burk, RF	Vanderbilt University	Selenium supplementation of patients with cirrhosis	CRISP 2001
Burk, RF	Vanderbilt University	Selenoprotein-P structure, function, and activity	CRISP 2001
Carlson, SG	National Institutes of Health	Antioxidant protection in age-associated atherosclerosis	FEDRIP 2002
Cassano, PA	Cornell University	Nutritional influences on lung disease	CRIS/UDSA 2001
Chirase, NK	Texas A&M University	Nutritional and environmental stress and immune response of feeder cattle	FEDRIP 2002
Chu, F-F	National Institutes of Health	Selenium-afforded protection against atherosclerosis	FEDRIP 2002
Clarke, LC	University of Arizona	Phase II chemoprevention trial of selenium and prostate cancer	CRISP 2002

3. HEALTH EFFECTS

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
Clarke, LC and Marshall, JR	University of Arizona	Randomized, controlled chemoprevention trials in populations at very high risk for prostate cancer: Elevated prostate-specific antigen and high-grade prostatic intraepithelial neoplasia	CRISP 2002
Cohen, HJ	Stanford University	Relationship of the synthesis and secretion of an extracellular selenium dependent glutathione peroxidase to changes in renal function	CRISP 2001
Cohen, HJ	Stanford University	Selenium nutrition—Effects on blood cell function	FEDRIP 2002
Coltman, CA	CTRC Research Foundation	Chemoprevention of prostate cancer	CRISP 2001
Combs, GF	Cornell University	Characterization of antioxidant status of a large cohort of free-living Americans	FEDRIP 2002
Combs, GF	Cornell University	Dietary selenium and maintenance of colonic health	FEDRIP 2002
Combs, GF	Cornell University	Metabolic events at extremes of selenium intake; characterization of antioxidant status of a large cohort of free-living Americans	CRIS/UDSA 2001
Combs, GF	Cornell University	Kinetics of organic and inorganic selenium during dietary supplementation	CRIS/UDSA 2001
Costello, AJ	University of Melbourne	A randomized, controlled chemoprevention trial of selenium in familial prostate cancer: Rationale, recruitment, and design issues	Costello 2001
Davis, CD	Agricultural Research Service	Role of selenium in cancer susceptibility	CRIS/UDSA 2001
Diamond, AM	University of Illinois	Mechanism by which selenium protects against mutagenesis	CRISP 2001
Diamond, AM	University of Illinois	Selenium, aminothiols, and radiation	CRISP 2002
Doolittle, JJ	South Dakota University	Bioavailability of nutrients and contaminants in soil	FEDRIP 2002
Driscoll, DM	Cleveland Clinic Foundation	Mechanism of selenoperoxidase biosynthesis	CRISP 2001
Driskell, JA	University of Nebraska	Nutrient bioavailability: A key to human nutrition	FEDRIP 2002
El-Bayoumy, KE	American Health Foundation	Chemoprevention of oral cancer: model studies	CRISP 2001
El-Bayoumy, KE	American Health Foundation	Chemoprevention of lung cancer by organoselenium: Model studies	CRISP 2002

3. HEALTH EFFECTS

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
El-Bayoumy, KE	American Health Foundation	Chemoprevention of mammary cancer by organoselenium	CRISP 2001
Fawzi, WW	National Institutes of Health	Trials of vitamins in HIV positive progression and transmission	FEDRIP 2002
Fiala, E	American Health Foundation	Organoselenium compounds as modifiers of initiation/postinitiation carcinogenesis	CRISP 2002
Finley, JW	University of North Dakota	Chemical forms of selenium in foods	FEDRIP 2002
Finley, JW	Oregon State University	Health benefits of high-selenium foods to humans	FEDRIP 2002
Funt, RC and Clinton, S	Ohio State University	Increasing the antioxidant level in Ohio berries for potential prevention and intervention of certain cancers in humans	FEDRIP 2002
Ganther, H	Roswell Park Memorial Institute	Selenium metabolism and anti-carcinogenic action	CRISP 2001
Ganther, H	University of Wisconsin	Organoselenium compounds biosynthesis and function	CRIS/UDSA 2001
Gesteland, RF	University of Utah	Genetic analysis of synthesis of selenium containing proteins	CRISP 2001
Gladyshev, VN	University of Nebraska	Biochemistry and molecular biology of selenium containing enzymes	CRIS/UDSA 2001
Gladyshev, VN	University of Nebraska	Identity of terminator and selenocysteine UGA codons	CRISP 2001
Glauert, HP	University of Kentucky	Effect of dietary antioxidants on hepatic NF-KB activation	CRIS/UDSA 2001
Gorbach, SL	Tufts University	Impact of micronutrients on progression of SIV	FEDRIP 2002
Gorbach, SL	Harvard University	Wasting, nutritional status, and micronutrients	FEDRIP 2002
Gottschall, EB	National Jewish Medical and Research Center	Randomized, placebo-controlled, double blind trial of asbestos-exposed workers using high selenium yeast supplementation	CRISP 2001
Gottschall, EB	National Jewish Medical and Research Center	Selenium and lung cancer risk in asbestos workers	CRISP 2002
Guttenplan, JB	New York University	Antimutagenesis by lycopene and selenium in rodents	CRISP 2001
Hakala TR	Department of Veterans Affairs	Select trial	FEDRIP 2002
Honn, KV	Wayne State University	Prostate cancer	FEDRIP 2002
Hurwitz, BE	University of Miami	Drug abuse, HIV, selenium supplementation, and CVD risk	FEDRIP 2002

3. HEALTH EFFECTS

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
Ip, C	Roswell Park Memorial Institute	Mammary cancer prevention by novel selenium compounds	CRISP 2002
James, LF	Agricultural Research Service	Livestock poisoning from <i>Astragalus</i> and <i>Oxytropis</i> species	CRIS/UDSA 2001
Johnson, JL	University of Nebraska	Interaction of trace minerals as related to prenatal supplementation of the pregnant beef cow	FEDRIP 2002
Kadlubar, F	Not available	Environmental and genetic epidemiology of colorectal adenomas	CRISP 2002
Karagas, M	Not available	Epidemiology of arsenic and other toxic metals	CRISP 2002
Kegley, EB and Kellogg, DW	University of Arkansas	Effect of trace mineral level and source on immune function and performance of weaned beef cattle	FEDRIP 2002
Kim, J	University of Texas MD Anderson Cancer Center	Feasibility study of L-selenomethionine in prevention of prostate cancer	CRISP 2001
Kiremidjian-Schumacher, L et al.	New York University, College of Dentistry	Dietary selenium and immunocompetence in the elderly	FEDRIP 2002
Klein, EA	Cleveland Clinic Foundation	SELECT: The selenium and vitamin E cancer prevention trial: Rationale and design	Klein et al. 2000
Kolonel, LN	University of Hawaii at Manoa	Biomarkers of prostate cancer risk in a multi-ethnic cohort	CRISP 2001
Kolonel, LN	University of Hawaii at Manoa	Epidemiologic studies of diet and cancer in Hawaii	CRISP 2001
Koutnik, V	University of Brno	Selenium in food chains and its impact on human health	CRIS/UDSA 2001
Lacourciere, G and Nhlbi, NIH	National Institutes of Health	Utilization of selenocysteine in selenophosphate biosynthesis	FEDRIP 2002
Lei, X	Cornell University	Antioxidative role of glutathione peroxidase in transgenic mice	CRISP 2001
Lei, XG et al.	Cornell University	Developing an organic selenium supplement for animal nutrition and environmental protection	FEDRIP 2002
Lei, XG et al.	Cornell University	Mineral nutrition in animal agriculture and environmental protection	FEDRIP 2002
Lemarchand, L	University of Hawaii	Phytochemicals and lung risk in a multi ethnic cohort	FEDRIP 2002
Levander, OA	Agricultural Research Service	Role of vitamin E and selenium in human health promotion	CRIS/UDSA 2001
Levander, OA	University of Maryland	Kinetics of organic and inorganic selenium during dietary supplementation	CRIS/UDSA 2001

3. HEALTH EFFECTS

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
Lewis, NS	California Institute of Technology	Picosecond dynamic studies of electron transfer rates as III-V semiconductor/liquid interfaces	FEDRIP 2002
Longnecker, M	National Institutes of Health	Validity of toenail element levels as a surrogate measure of exposure	CRISP 2002
Mahan, DC	Ohio State University	Mineral and vitamin nutrition of swine	FEDRIP 2002
Mark, S	Not available	Intervention trials and related studies	CRISP 2002
Marshall, JR	University of Arizona	Phase II chemoprevention trial of selenium and prostate cancer	CRISP 2002
May, JM	Vanderbilt University	Antioxidant interactions of selenium and vitamins C and E	CRISP 2001
Medina, D	Roswell Park Memorial Institute	Selenoproteins in rat mammary tumorigenesis	CRISP 2001
Medina, D	Roswell Park Memorial Institute	Selenium modified gene expression in the carcinogen treated mammary gland	CRISP 2002
Morgan, DL	National Institutes of Health	Toxicity of chemicals used in the semiconductor industry	FEDRIP 2002
Nomura, AM	Kuakini Medical Center	Cancer epidemiology of migrant Japanese in Hawaii	CRISP 2001
Ogasawara, Y and Nhlbi, NIH	National Institutes of Health	Properties of selenotrisulfides and perselenides	FEDRIP 2002
Page, JG	Not available	Thirteen week oral toxicity study of 1,4-phenylenebis (methylene) selenocyanate	CRISP 2002
Palmer, IS	South Dakota University	Biochemistry of selenium	FEDRIP 2002
Pence, BC	Texas Technical University Health Sciences Center	Induction by selenium of the antioxidant and the prooxidant, apoptotic pathways in cultured cells	CRISP 2001
Penland, JG	Department of Agriculture	Mineral element nutrition, neuropsychological function and behavior	FEDRIP 2002
Powis, G	University of Arizona	Thioredoxin reductases and cancer	CRISP 2001
Prolla, TA	University of Wisconsin	Role of dietary selenium in intestinal tumorigenesis	CRISP 2001
Rao, L	University of Wisconsin	Genetic characterization of the selenoenzyme phospholipids-hydroperoxide glutathione peroxidase	CRISP 2001
Reddy, BS	American Health Foundation	Chemoprevention of colon cancer by organoselenium compounds	CRISP 2002
Reddy, CC	Pennsylvania State University	Antioxidant effects on prostaglandin metabolism, lipid peroxidation, and immunologic defense	CRIS/UDSA 2001

3. HEALTH EFFECTS

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
Repine, JE	Department of Veterans Affairs	Effect of NAC and/or selenium on blood markers of oxidative stress and inflammation	FEDRIP 2002
Roberts, JC	University of Utah	Advances in selenium supplementation	CRISP 2002
Roughead, ZK	Department of Agriculture	Biomarkers for assessment of human mineral nutritional status and requirements	FEDRIP 2002
Roy, M	New York University	Selenium supplementation and immunocompetence in the elderly	CRIS/UDSA 2001
Sampliner, RE	Department of Veterans Affairs	Phase III study of the effects of celecoxib, selenium, or the combination on adenomatous polyp recurrence in adenomatous polyp patients	FEDRIP 2002
Sevanian, A	University of Southern California	Oxidant stress and atherogenicity of oxidized LDL	FEDRIP 2002
Shearer, TR	Oregon Health & Science University	Mechanism of selenium induced cataract	FEDRIP 2002
Simoneau, AR	Department of Veterans Affairs	Selenium in prostate cancer	FEDRIP 2002
Smith, AM	Ohio State University	Influence of gender and life cycle on selenium requirements and metabolism	CRIS/UDSA 2001
Sordillo, LM	Pennsylvania State University	Oxidant stress and endothelial cell metabolism	FEDRIP 2002
Sordillo, LM	Pennsylvania State University	Mechanisms of endothelial cell dysfunction during selenium deficiency	FEDRIP 2002
Stadtman, TC and Nihbli, NIH	National Institutes of Health	Selenium biochemistry	FEDRIP 2002
Stampfer, MJ	National Cancer Institute	Nutritional and biochemical markers of cancer	FEDRIP 2002
Stampfer, MJ	Harvard University	Prospective study of diet and bladder cancer	FEDRIP 2002
Sunde, RA	University of Missouri	New essential roles for selenium; regulatory elements of selenium-dependent peroxidases; regulatory elements of the rat glutathione peroxidase gene	CRIS/UDSA 2001
Sunde, RA	University of Missouri	Glutathione peroxidases: Selenium requirement and function	FEDRIP 2002
Taylor, JR	Department of Veterans Affairs	Prevention of non-melanoma skin cancer with a nutritional supplementation of selenium	FEDRIP 2002
Taylor, EW	University of Georgia	Selenoproteins, NF-KB, and HIV disease in drug users	CRISP 2001

3. HEALTH EFFECTS

Table 3-8. On-going Studies on Selenium Health Effects

Investigator	Institute	Research area	Reference
Terris, MK	Department of Veterans Affairs	Blood and tissue sampling in prostate ultrasound patients	FEDRIP 2002
Terris, MK	Department of Veterans Affairs	Phase II study of the effect of selenium supplementation on the progression of prostate cancer	FEDRIP 2002
Thompson, I	University of Texas Health Science Center San Antonio	Biomarkers of risk for prostate cancer	CRISP 2001
Thompson, H	Roswell Park Memorial Institute	Mechanisms of selenium anticancer and toxic activities	CRISP 2001
Thompson, H	Roswell Park Memorial Institute	Selenium and lung cancer risk	CRISP 2002
Turnlund, JR et al.	Department of Agriculture	Influence of dietary intervention on mineral homeostasis	FEDRIP 2002
Turnlund, JR et al.	Department of Agriculture	Trace element metabolism, status and requirements of humans	FEDRIP 2002
Veillon, C	Agricultural Research Service	Metabolism, function, and interactions of selenium using stable isotopes	CRIS/USDA 2001
Weiss, GR	Department of Veterans Affairs	Pilot study of 1-selenomethionine in prostate cancer patients scheduled to undergo radical prostatectomy	FEDRIP 2002
Weiss, SL	University of Missouri	Molecular basis for selenium regulation of glutathione peroxidase mRNA	CRIS/USDA 2001
Whanger, PD	Oregon State University	Effect of selenium on selenoproteins in human muscle and brain cells	FEDRIP 2002
Whanger, PD	Oregon State University	Metabolic function of selenoprotein	CRISP 2001
Whanger, P	Oregon State University	Role of selenium and vitamin E in scour and immunity of newborn calves; influence of pregnancy on selenium metabolism in women of low selenium status; metabolic relationship between selenium and myopathy	CRIS/USDA 2001
Yu, MC	University of Southern California	Singapore cohort study of diet and cancer	CRISP 2001

CRIS = Current Research Information System; CRISP = Computer Retrieval of Information on Science Projects; FEDRIP = Federal Research in Progress; NCI = National Cancer Institute; NIH = National Institutes of Health; USDA = US Department of Agriculture

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of selenium and selenium compounds is presented in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Selenium is a non-metal element with atomic number 34 and an atomic mass of 78.96 (Lide 2000). Selenium belongs to Group 6 (Group VIA) of the periodic table, located between sulfur and tellurium, and resembles sulfur both in its various forms and in its compounds. The six stable isotopes of selenium are ^{74}Se , ^{76}Se , ^{77}Se , ^{78}Se , ^{80}Se , and ^{82}Se . These isotopes occur naturally with approximate abundances of 0.87, 9.02, 7.58, 23.52, 49.82, and 9.19%, respectively (Hoffmann and King 1997). Artificial radioactive isotopes of selenium have also been created by neutron activation. The gamma-emitting isotope ^{75}Se has been used in diagnostic applications of medicine (Hoffmann and King 1997). Selenium exists in several allotropic forms. Three are generally recognized, but as many as six have been claimed (Lide 2000). The stable form at ordinary room temperatures is the grey or hexagonal form with a melting point of 220.5 °C (Lide 2000). The other two important forms are red (monoclinic) with a melting point of 221 °C and amorphous selenium, which exists in black and red forms. Black amorphous selenium is vitreous and is formed by the rapid cooling of liquid selenium. Red amorphous selenium is colloidal and is formed in reduction reactions (Hoffmann and King 1997). Important selenium oxidation states are -2, 0, +4, and +6.

The chemical properties of selenium are similar to sulfur. Selenium combines with metals and many nonmetals directly or in aqueous solution. The selenides resemble sulfides in appearance, composition, and properties (Hoffmann and King 1997). Selenium may form halides by reacting vigorously with fluorine and chlorine, but the reactions with bromine and iodine are not as rapid. Selenium does not react directly with hydrogen fluoride or hydrogen chloride, but decomposes hydrogen iodide to liberate iodine and yield hydrogen selenide (Hoffmann and King 1997). Selenium reacts with oxygen to form a number of oxides, the most stable of which is selenium dioxide.

Information regarding the physical and chemical properties of selenium and selenium compounds is located in Table 4-2.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Selenium and Selected Compounds^a

Characteristic	Selenium	Hydrogen selenide	Selenic acid	Selenious acid
Synonyms	Elemental selenium; selenium base; selenium dust; colloidal selenium; selenium homopolymer ^b ; selenium alloy	Dihydrogen selenide; hydrogen selenide [H ₂ Se]; selenium anhydride; selenium dihydride; selenium hydride; selane	Selenic acid, liquid ^{DOT,b}	Monohydrated selenium dioxide; selenous
Registered trade name(s)	C.I. 77805; VANDEX ^b			
Chemical formula	Se	H ₂ Se	H ₂ SeO ₄	H ₂ SeO ₃
Wisewesser line notation	SE	H2 SE	H2.SE-04	H2SE-03
Identification numbers:				
CAS	7782-49-2	7783-07-5	7783-08-6	7783-00-8
NIOSH RTECS	VS7700000	MX1050000	VS6575000	VS7175000
EPA hazardous waste	No data	No data	No data	U204 ^c
OHM/TADS	7216880	No data	No data	No data
DOT/UN/NA/IMCO shipping	UN 2658 ^b	UN 2202; Hydrogen selenide; anhydrous	UN 1905; IMCO 8.0	No data
HSDB	4493	548	675	6065
NCI	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Selenium and Selected Compounds^a

Characteristic	Sodium selenate	Potassium selenate	Sodium selenide	Sodium selenite
Synonyms	Disodium selenate	Selenic acid, dipotassium salt ^b	Disodium monoselenide ^b	Disodium selenite; disodium selenium trioxide; selenious acid disodium salt; sodium selenium oxide
Registered trade name(s)	P-40 ^b ; Sel-Tox SS02 and SS-20 ^c	No data	No data	
Chemical formula	Na ₂ SeO ₄ ^d	K ₂ SeO ₄	Na ₂ Se ^b	Na ₂ SeO ₃ ^d
Wisewesser line notation	NA2 SE-04 ^b	KA2 SE-04	NA2 SE	NAS SE-03
Identification numbers:				
CAS	13410-01-0	7790-59-2	1313-85-5 ^b	10102-18-8
NIOSH RTECS	No data	VS6600000	WE0350000 ^b	VS7350000
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	7217299
DOT/UN/NA/IMCO shipping	No data	No data	No data	UN 2630 ^b
HSDB	No data	No data	No data	768
NCI	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Selenium and Selected Compounds^a

Characteristic	Selenium dioxide	Selenium trioxide	Selenocystine	Selenomethionine
Synonyms	Selenious anhydride; selenium oxide; selenium oxide [SeO ₂]; selenous acid anhydride	No data	Selenium cystine ^b ; 3,3-diselenodi-DL-alanine ^b ; seleno-DL-cystine ^b ; DL-selenocystine ^b	Methionine, seleno ^b ; 2-amino-4-(methylselenyl) butyric acid; 2-amino-4-(methylsel eno)
Registered trade name(s)	No data	No data		
Chemical formula	SeO ₂	SeO ₃ ^e	C ₂ H ₄ NO ₂ (CH ₂)Se 2(CH ₂)C ₂ H ₄ NO ₂	(CH ₃)Se(CH ₂)2C ₂ H ₄ NO ₂
Identification numbers:				
CAS	7446-08-04	13768-86-0 ^f	1464-43-3 ^b	1464-42-2
NIOSH RTECS	VS8575000	No data	AY6030000 ^b	ES100000
EPA hazardous waste	V204 ^c	No data	No data	No data
OHM/TADS	7800105	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	677	No data	No data	No data
NCI	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Selenium and Selected Compounds^a

Characteristic	Selenium sulfide	Selenium disulfide
Synonyms	Selenium monosulfide; selenium sulfide [SeS]; selensulfid (German); sulfur selenide (SSe)	Selenium disulphide; selenium sulfide ^b ; sulfur selenide
Registered trade name(s)	No data	Exsel; Selsun Blue; Selsum ^b ; Seleen
Chemical formula	SeS	SeS ₂ ^b
Wisewesser line notation	SE S	SE S2 ^b
Identification numbers:		
CAS	744-34-6	7488-56-4
NIOSH RTECS	VTO525000	VS8925000
EPA hazard waste	V205 ^b	V205
OHM/TADS	8400272	8400272
DOT/UN/NA/IMCO shipping	No data	UN 2657
HSDB	679	No data
NCI	NCI-C50033	No data

^aAll information obtained from HSDB 2001, except where noted^bRTECS 2001^cEPA 1980a, 1980b (40 CFR 261.33)^dBudavari et al. 1996^eLide 2000^fChemIDplus 3003

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Selenium and Selenium Compounds^a

Property	Selenium	Hydrogen selenide	Selenic acid	Selenious acid
Molecular weight	78.96	80.98	144.97	128.97
Color/form	Red, grey, or black	Colorless ^b	White hexagonal prisms; hygroscopic ^b	White hygroscopic prisms ^b
Physical state	Solid	Gas	Solid	Solid
Melting point	221 °C (red); 220.5 °C (grey); 180 °C (black) ^b	-65.73 °C	58 °C	70 °C (decomposes) ^b
Boiling point	685 °C	-41.3 °C	260 °C	None, loses water upon heating
Density (g/cm ³)	4.39 (red); 4.81 (grey); 4.28 (black) ^b	2.12 (-42 °C)	2.9508 (15 °C)	3.004 (15 °C)
Odor	Unknown; upon combustion, smells like rotten horseradish	Disagreeable odor	No data	No data
Odor threshold: Water (mg/m ³)	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility: Water	Insoluble	377 mL/100 mL at 4 °C; 270 mL/100 mL at 22.5 °C; 0.73 mL/100 mL at 20 °C ^c	Very soluble in hot water	90 parts dissolve in 100 parts of water at 0 °C; 400 parts in 100 parts at 90 °C
Organic solvent(s)	Insoluble in alcohol, slightly soluble in carbon disulfide (2 mg/100 mL, room temperature), soluble in ether	Soluble in carbon disulfide, carbonyl chloride	Decomposes in alcohol ^b	Very soluble in alcohol
Partition coefficients: Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 356 °C (grey)	1,330 mmHg at -30 °C; 3,420 mmHg at 0.2 °C; 9,120 mmHg at 30.8 °C	No data	2 mmHg at 15 °C; 4.5 mmHg at 33 °C; 7 mmHg at 40.3 °C
Henry's Law constant	Not applicable	No data	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Selenium and Selenium Compounds^a

Property	Selenium	Hydrogen selenide	Selenic acid	Selenious acid
Flashpoint	No data	Not applicable	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	ppm selenium to mg Selenium/m ³ in air (20 °C): ppm selenium x 3.23=mg selenium/m ³ to ppm selenium in air (20 °C): mg selenium/m ³ x 0.31=ppm selenium (v/v)	No data	No data
Explosive limits	Unknown ^d	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Selenium and Selenium Compounds^a

Property	Sodium selenate	Potassium selenate	Sodium selenide	Sodium selenite
Molecular weight	188.94	221.15	124.94	172.94
Color/form	White crystals	Colorless crystals or white powder	Crystalline; turns red on exposure to air and deliquesces	White tetragonal crystals ^b
Physical state	Solid	Solid	Solid	Solid
Melting point	No data	No data	>875 °C	No data
Boiling point	No data	No data	No data	No data
Density (g/cm ³)	1.61 ^b	3.07	2.625 (10 °C)	No data
Odor	No data	No data	No data	No data
Odor threshold: Water (mg/m ³)	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility: Water	Very soluble in water	Soluble in about 1 part of water	Decomposes in water	Freely soluble in water
Organic solvent(s)	No data	No data	No data	No data
Partition coefficients: Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's Law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	Not flammable ^e	Not flammable ^e
Flashpoint	No data	No data	Not flammable ^e	Not flammable ^e
Flammability limits	No data	No data	Not flammable ^e	Not flammable ^e
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Selenium and Selenium Compounds^a

Property	Selenium dioxide	Selenium trioxide	Selenocystine	Selenomethionine
Molecular weight	110.96	126.96 ^b	334.12 ^c	196.11
Color/form	Lustrous, tetragonal needles; yellowish-green vapor	White crystals ^b	No data	Transparent, hexagonal sheets or plates; metallic luster or crystals
Physical state	Solid	Solid	No data	Solid
Melting point	340 °C; sublimes at 315 °C ^b	118 °C ^b	No data	DL form: 265 °C (decomposes); L form: 266–268 °C
Boiling point	None ^b	Sublimes ^b	No data	Not applicable
Density (g/cm ³)	3.954 (15 °C)	3.44 ^b	No data	No data
Odor	Pungent sour smell	No data	No data	No data
Odor threshold: Water (mg/m ³)	0.0002 ^e	No data	No data	No data
Air	No data	No data	No data	No data
Solubility: Water (g/100 mL)	38.4 at 14 °C;	Soluble in water	No data	No data
Organic solvent(s) (parts/100 parts solvent)	in methanol: 10.16 at 11.8 °C; in 93% ethanol: 6.67 at 14 °C; in acetone: 4.35 at 15.3 °C; in acetic acid: 1.11 at 13.9 °C; soluble in benzene	No data	No data	No data
Partition coefficients: Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	12.5 mm Hg at 70 °C; 20.2 mm Hg at 94 °C; 39.0 mm Hg at 181 °C; 760 mm Hg at 315 °C; 848 mm Hg at 320 °C	No data	No data No data	No data No data
Henry's Law constant	Not applicable	Not applicable	No data	No data
Autoignition temperature	Not flammable ^e	Not flammable ^e	No data	No data
Flashpoint	Not flammable ^e	Not flammable ^e	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Selenium and Selenium Compounds^a

Property	Selenium dioxide	Selenium trioxide	Selenocystine	Selenomethionine
Flammability limits	Not flammable ^e	Not flammable ^e	No data	No data
Conversion factors	ppm (v/v) to mg/m ³ in air (20 °C): ppm (v/v) x 4.53=mg/m ³ ; mg/m ³ to ppm (v/v) in air (20 °C): mg/m ³ x 0.22=ppm (v/v)	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Selenium and Selenium Compounds^a

Property	Selenium sulfide	Selenium disulfide
Molecular weight	111.02 ^f	143.08 ^f
Color/form	Orange-yellow tablets or powder ^f	Bright red-yellow powder ^f
Physical state	Solid ^f	Solid ^f
Melting point	118–119 °C (decomposes) ^f	<100 °C ^f
Boiling point	No data	No data
Density (g/cm ³)	3.056 (0 °C) ^f	No data
Odor	No data	No data
Odor threshold:		
Water (mg/m ³)	No data	No data
Air	No data	No data
Solubility:		
Water	Insoluble	Insoluble
Organic solvent(s)	Insoluble in ether; decomposes in alcohol ^f	No data
Partition coefficients:		
Log K _{ow}	Not applicable	No data
Log K _{oc}	Not applicable	No data
Vapor pressure	Not applicable	Not applicable
Henry's Law constant	Not applicable	Not applicable
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

^aAll information obtained from Budavari et al. 1996, unless otherwise noted.^bLide 2000^cRTECS 2001^dNIOSH/OSHA 1981^eWeiss 1986^fLide 1993

Note: The gray metallic form is the most stable form of selenium (Budavari et al. 1996).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Selenium is distributed widely in nature and is found in most rocks and soils at concentrations between 0.1 and 2.0 ppm (Fishbein 1983). However, elemental selenium is seldom found naturally, but it is obtained primarily as a byproduct of copper refining (Fishbein 1983). Selenium is contained in the constituents of the copper anode that are not solubilized during the copper refining process and ultimately accumulate on the bottom of the electrolytic tank. These constituents, usually referred to as slimes, contain roughly 5–25% selenium and 2–10% tellurium. Selenium is commercially produced by either soda ash roasting or sulfuric acid roasting of the copper slimes.

Soda Ash Roasting. A soda ash binder is mixed with the slimes and water to form a stiff paste. The paste is extruded or pelletized and allowed to dry and then roasted at 530–650 °C. The roasted product is then ground and leached into water. The resultant hexavalent selenium dissolves as sodium selenate, Na_2SeO_4 . The sodium selenate may be reduced by controlled heating to sodium selenide, which is leached with water to form a liver-red solution of sodium selenide that is readily oxidized to the elemental form by blowing air through the solution (Hoffmann and King 1997). A second process for the reduction of hexavalent selenium involves the use of concentrated hydrochloric acid or ferrous iron salts catalyzed by chloride ions as the reductant (Hoffmann and King 1997).

Sulfuric Acid Roasting. In this method, the copper slimes are mixed with sulfuric acid and roasted at 500–600 °C to produce selenium dioxide, which volatilizes readily at the roasting temperature. The selenium dioxide is reduced to elemental selenium during the scrubbing process with sulfur dioxide and water. The resultant commercial-grade selenium can be purified to 99.5–99.7% (Hoffmann and King 1997).

The U.S. production of selenium was 373 and 379 metric tons in 1995 and 1996, respectively (USGS 2001, 2002). No production data were reported for the years 1997–2001. All of the primary selenium producers in the United States are electrolytic copper refiners. Asarco Incorporated and Kennecott Utah Copper Corporation produce refined selenium in the United States (Hoffmann and King 1997; SRI 2000). Two other copper refiners, Phelps Dodge Corporation and Magma Copper Company, send selenium or

selenium-bearing copper slimes outside of the United States for final processing (Hoffmann and King 1997).

Tables 5-1 and 5-2 list facilities in each state that produce, process, or import selenium and selenium compounds, respectively, for commercial use. The data do not include facilities such as electric power generating plants that release selenium unintentionally as a by-product. The intended use and the range of maximum amounts of these substances that are stored on site are also included. The data listed in these tables are derived from the Toxics Release Inventory (TRI00 2002). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

5.2 IMPORT/EXPORT

The import volumes of selenium were 324, 428, 346, 339, 326, 452, and 500 metric tons for 1995, 1996, 1997, 1998, 1999, 2000, and 2001, respectively (USGS 2001, 2002). The U.S. exports of selenium were 270, 322, 127, 151, 233, 89, and 75 metric tons for 1995, 1996, 1997, 1998, 1999, 2000, and 2001, respectively (USGS 2001, 2002).

5.3 USE

In electronics, selenium's semiconductor and photoelectric properties make it useful in "electric eyes," photographic exposure meters, and rectifiers for home entertainment equipment. In addition, a large proportion of the available selenium is used to coat the metal cylinders from which a photographic image is transferred in xerography (Fishbein 1983). Selenium is widely used in the glass industry to counter coloration that results from iron impurities. It is also used in the production of both red and black glasses (Fishbein 1983). Selenium is contained in pigments that are used in plastics, paints, enamels, inks, and rubber (Fishbein 1983). Selenium is used as a catalyst in the preparation of pharmaceuticals including niacin and cortisone, as an ingredient in antidandruff shampoos (selenium sulfide), and as a constituent of fungicides (selenium sulfide) (IARC 1975a). Radioactive selenium is used in diagnostic medicine and aids in the visualization of difficult-to-study malignant tumors (Fishbein 1983; Jereb et al. 1975). Selenium is contained in some dietary supplements at concentrations in the range of 10–25 µg/tablet (Goodman et al. 1990). Selenium is also used as a nutritional feed additive for poultry and livestock, in pesticide formulations, and as an accelerator and vulcanizing agent in rubber production (Fishbein 1983; NAS 1976a). Table 5-3 lists some specific uses of selected selenium compounds.

5. PRODUCT IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Selenium

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AZ	1	1,000	9,999	12
CA	2	100	99,999	12
IA	1	100	999	7
IL	1	1,000	9,999	7
IN	2	100,000	999,999	8
LA	1	1,000	9,999	12
MI	1	0	99	12
OK	1	100	999	1, 5
OR	1	100,000	999,999	12
PA	2	10,000	99,999	6, 8
SC	1	10,000	99,999	1, 3, 4, 5, 9, 12, 13
WA	1	100	999	14
WY	1	0	99	1, 13

Source: TRI00 2002

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

5. PRODUCT IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Selenium Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	4	100	99,999	1, 3, 4, 5, 8, 9, 12, 13
AR	1	10,000	99,999	12
AZ	2	10,000	999,999	1, 3, 4, 5, 9, 13, 14
CA	1	10,000	99,999	8, 9
FL	1	1,000	9,999	1, 5, 9, 12, 13, 14
GA	5	1,000	99,999	1, 2, 3, 4, 5, 6, 9, 13
IA	2	100	9,999	3, 4, 7, 8
ID	1	100,000	999,999	1, 5
IL	3	1,000	99,999	1, 5, 7, 12, 13
IN	4	0	99,999	1, 5, 7, 9, 12, 13
KY	5	100	99,999	1, 3, 4, 5, 9, 12, 13
LA	1	10,000	99,999	1, 3, 4, 5, 6, 8
MA	1	10,000	99,999	1, 5
MD	2	1,000	99,999	1, 3, 4, 5, 6, 13
MI	4	1,000	999,999	1, 2, 3, 4, 5, 8, 9, 12, 13
MN	1	1,000	9,999	1, 2, 9, 13, 14
MO	1	10,000	99,999	7
MT	1	10,000	99,999	1, 5, 12, 14
NC	3	10,000	99,999	1, 3, 4, 5, 9, 12, 13, 14
NM	4	0	99,999	1, 3, 4, 5, 9, 12, 13
NV	6	10,000	9,999,999	1, 5, 6, 10, 13, 14
OH	8	1,000	9,999,999	1, 3, 4, 5, 7, 9, 12, 13, 14
OK	1	1,000	9,999	8
PA	8	0	999,999	1, 4, 5, 6, 9, 12, 13, 14
SC	1	10,000	99,999	1, 3, 4, 5, 9, 12, 13
TN	2	1,000	99,999	1, 5
TX	10	10,000	999,999	1, 2, 3, 4, 5, 6, 8, 9, 12, 14
UT	4	10,000	9,999,999	1, 3, 4, 5, 6, 9, 12, 13
VA	1	10,000	99,999	1, 5
WV	9	100	99,999	1, 3, 4, 5, 9, 12, 13, 14
WY	2	0	99,999	1, 4, 5, 9, 12, 13

Source: TRI00 2002

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct

6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging

11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

5. PRODUCT IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-3. Some Selenium Compounds and Their Uses^a

Compound	Use
Elemental selenium	In rectifiers, photoelectric cells, blasting caps, xerography, stainless steel; as a dehydrogenation-catalyst
Sodium selenate (Na_2SeO_4)	As an insecticide; in glass manufacture; in medicinals to control animal diseases
Sodium selenite (Na_2SeO_3)	In glass manufacture; as a soil additive for selenium-deficient areas
Selenium diethyldithio-carbamate	Fungicide; vulcanizing agent
Selenium disulfide (SeS_2)	In veterinary medicine
Selenium sulfide (SeS)	In anti-dandruff shampoos and in veterinary medicine
Selenium dioxide (SeO_2)	Catalyst for oxidation, hydrogenation, or dehydrogenation of organic compounds
Selenium hexafluoride (SeF_6)	As a gaseous electric insulator
Selenium oxychloride (SeOCl_2)	Solvent for sulfur, selenium, tellurium, rubber, bakelite, gums, resins, glue, asphalt, and other materials
Aluminum selenide (Al_2Se_3)	Preparation of hydrogen selenide for semi-conductors
Ammonium selenite [(NH_4) $_2\text{SeO}_3$]	Manufacture of red glass
Cadmium selenide	Photoconductors, photoelectric cells, rectifiers
Cupric selenate (CuSeO_4)	In coloring copper and copper alloys
Tungsten diselenide (WSe_2)	In lubricants

^aAdapted from Fishbein 1983

The 2002 consumption patterns for selenium by industry were as follows: glass manufacturing, 35%; chemicals and pigments, 20%; electronics, 12%; and miscellaneous (including agriculture and metallurgy), 33% (USGS 2002).

5.4 DISPOSAL

Selenium was listed by EPA in 1973 as a nonradioactive hazardous element and, as such, is subject to many regulations (Dawson and Mercer 1986). Selenium compounds should be stored in a dry area to avoid contamination of water with selenium and to decrease the hazards that may result from human exposure to selenium-contaminated water (ITII 1976).

Disposal and waste treatment consist of treating an acidified solution of selenium with sodium sulfite to form the reducing agent sulfur dioxide. The selenium solution is then heated to produce elemental selenium, which is less mobile in the environment and less bioavailable, and the solution is filtered and washed (ITII 1976).

According to the TRI, in 2000, an estimated 76,248 pounds of elemental selenium and 1,782,654 pounds of selenium compounds were transferred off-site, presumably for disposal (TRI00 2002).

6. POTENTIAL FOR HUMAN EXPOSURE

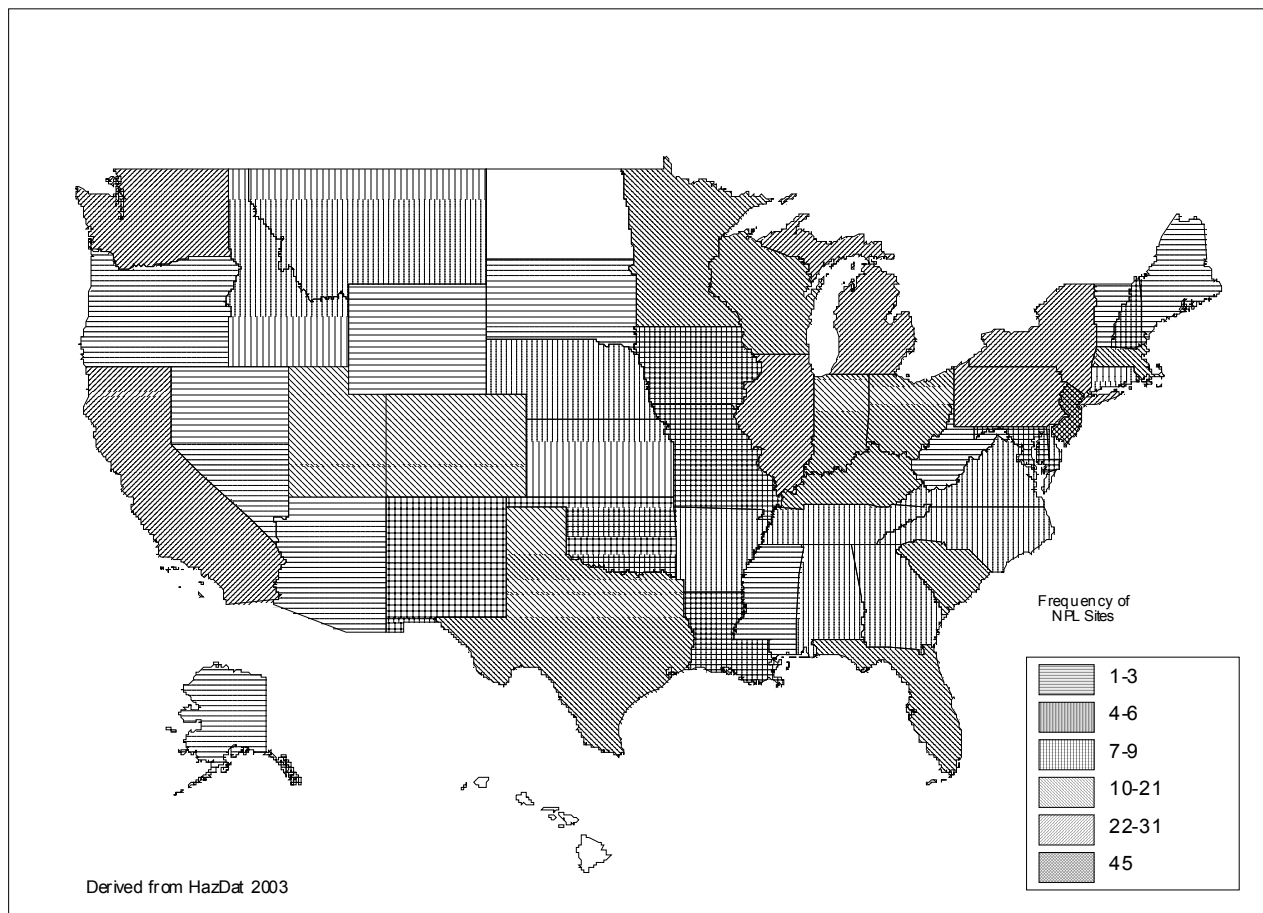
6.1 OVERVIEW

Selenium has been identified in at least 508 of the 1,623 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for selenium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 502 are located within the United States, 4 are located in the Commonwealth of Puerto Rico, 1 is located in Guam, and 1 is located in the U.S. Virgin Islands (not shown).

Selenium is ubiquitous in the environment, being released from both natural and anthropogenic sources. The principal releases of selenium into the environment as a consequence of human activities result from the combustion of coal. Workers in the metals industry and health services, mechanics, and painters may be exposed to higher levels of selenium than the general population or persons employed in other trades. For the general population, the primary exposure pathways, in order of decreasing relative proportions, are food, water, and air. The relative proportions of these exposure pathways at hazardous waste sites are not known. Although selenium has been reported at hazardous waste sites, analysis on specific forms has not been performed. In air, selenium dioxide, methyl selenide, and dimethyl selenide are the most prevalent forms found in the atmosphere. Selenates and selenites are water soluble and, thus, can be found in water sources. Salts of selenic and selenious acids are most likely to be found in surface water and water contained in soil. Selenium sulfides would not be expected to be found at most hazardous waste sites, since they are usually manufactured for use in shampoos. Natural sources of selenium include the weathering of selenium-containing rocks to soils and volcanic eruptions.

The primary factor determining the fate of selenium in the environment is its oxidation state. Selenium is stable in four valence states (-2, 0, +4, and +6) and forms chemical compounds similar to those of sulfur. The heavy metal selenides (-2) are insoluble in water, as is elemental selenium. The inorganic alkali selenites (+4) and selenates (+6) are soluble in water (Weast 1988) and are therefore more bioavailable. Conditions such as pH (negative log hydrogen ion concentration), Eh (oxidation-reduction potential), and the presence of metal oxides affect the partitioning of the various compounds of selenium in the environment. In general, elemental selenium is stable in soils and is found at low levels in water because of its ability to coprecipitate with sediments. The soluble selenates are readily taken up by plants and

6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with Selenium Contamination

converted to organic compounds such as selenomethionine, selenocysteine, dimethyl selenide, and dimethyl diselenide. Selenium is bioaccumulated by aquatic organisms and may also biomagnify in aquatic organisms.

6.2 RELEASES TO THE ENVIRONMENT

The greatest proportion of selenium released to the environment as a consequence of regulated human activities is in coal fly ash, resulting from coal combustion. Anthropogenic emission sources of atmospheric selenium include coal and oil combustion facilities, selenium refining factories, base metal smelting and refining factories, mining and milling operations, and end-product manufacturers (e.g., some semiconductor manufacturers). Natural atmospheric releases of selenium result from volatilization of selenium by plants and bacteria, and from volcanic activity. Some selenium is released to water via sewage effluent, agricultural runoff, and industrial waste water. Selenium is released to soil primarily by leaching and weathering of the parent bedrock material, although dry and wet deposition also contribute to soil selenium levels.

According to the Superfund Amendments and Reauthorization Act (SARA), Section 313, Toxic Release Inventory (TRI00 2002), an estimated total of 264,267 pounds of elemental selenium was released to air, water, land, or injected underground from manufacturing and processing facilities in the United States in 2000 (see Table 6-1). In addition, 7,870,609 pounds of selenium compounds were released to air, water, land, or injected underground in 2000 (see Table 6-2). These data include all facilities that manufacture, import, and process selenium and selenium compounds as well as facilities (electric generating facilities, petroleum facilities, etc.) with unintentional releases to the environment. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

Combustion of coal and other fossil fuels is the primary source of airborne selenium compounds. In air, elemental selenium burns to form selenium dioxide; however, during the combustion of fossil fuels, essentially all of the selenium dioxide produced should be reduced to elemental selenium by the sulfur dioxide that results from the combustion of these materials (NAS 1976a). Estimates of the quantity of selenium released to the air from fossil fuel combustion vary. Estimated annual selenium air emissions

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Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Selenium

Reported amounts released in pounds per year ^a								
State ^b	Number of facilities	Air ^c	Water	Under-ground injection	Land	Total on-site release ^d	Total off-site release ^e	Total on and off-site release
AZ	1	No data	No data	No data	No data	No data	71,747	71,747
CA	2	1	0	No data	35,848	35,849	10	35,859
IA	1	No data	No data	No data	27	27	339	366
IL	3	109	19	No data	1	129	231	360
IN	3	0	No data	No data	2,260	2,260	2,056	4,316
LA	2	No data	No data	40,246	No data	40,246	No data	40,246
MI	1	5	No data	No data	No data	5	5	10
OK	1	No data	250	No data	250	500	No data	500
OR	1	0	No data	No data	112,600	112,600	1	112,601
PA	2	61,437	750	No data	No data	62,187	1,857	64,044
SC	1	3,929	No data	No data	6,533	10,462	No data	10,462
WA	1	No data	No data	No data	2	2	2	4
WY	1	No data	No data	No data	No data	No data	0	0
Total	25	65,481	1,019	40,246	157,521	264,267	76,248	340,515

Source: TRI00 2002

^aData in TRI are maximum amounts released by each facility.^bPost office state abbreviations are used.^cThe sum of fugitive and stack releases are included in releases to air by a given facility.^dThe sum of all releases of the chemical to air, land, water, and underground injection wells.^eTotal amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Selenium Compounds

Reported amounts released in pounds per year ^a								
State ^b	Number of facilities	Air ^c	Water	Under-ground injection	Land	Total on-site release ^d	Total off-site release ^e	Total on and off-site release
AL	4	15,545	4,125	No data	33,253	52,923	1,069	53,992
AR	1	546	No data	No data	No data	546	7,493	8,039
AZ	2	505	0	No data	820,005	820,510	2,265	822,775
CA	1	5	No data	No data	No data	5	No data	5
FL	2	7,105	No data	No data	362	7,467	3	7,470
GA	6	72,273	1,037	No data	43,067	116,377	10	116,387
IA	5	No data	No data	No data	No data	No data	No data	0
ID	1	1,849	No data	No data	98,184	100,033	5	100,038
IL	7	56	No data	No data	0	56	81,940	81,996
IN	5	4,427	1,871	No data	9,665	15,963	7,739	23,702
KY	5	19,750	14,200	No data	41,051	75,001	No data	75,001
LA	1	192	0	No data	No data	192	45,241	45,433
MA	1	234	100	No data	580	914	7,440	8,354
MD	2	16,001	360	No data	720	17,081	1,262	18,343
MI	4	16,408	2,417	No data	2,758,596	2,777,421	897,981	3,675,402
MN	2	255	2,400	No data	No data	2,655	265	2,920
MO	2	250	No data	No data	No data	250	250	500
MT	1	250	0	No data	13,000	13,250	250	13,500
NC	4	56,017	1,092	No data	27,080	84,189	10	84,199
NM	4	1,056	0	No data	91,282	92,338	24,300	116,638
NV	6	2,400	40	0	1,174,514	1,176,954	0	1,176,954
OH	9	71,941	16,635	No data	74,622	163,198	46,858	210,056
OK	1	9,000	No data	No data	No data	9,000	50	9,050
PA	8	39,509	2,093	No data	23,500	65,102	40,199	105,301
SC	1	4,174	No data	No data	11,605	15,779	No data	15,779
TN	2	14,010	4,600	No data	21,550	40,160	5	40,165

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Selenium Compounds

Reported amounts released in pounds per year ^a								
State ^b	Number of facilities	Air ^c	Water	Under-ground injection	Land	Total on-site release ^d	Total off-site release ^e	Total on and off-site release
TX	12	131,637	22	27,699	197,164	356,522	609,353	965,875
UT	4	4,122	1,000	No data	1,635,235	1,640,357	263	1,640,620
VA	1	4,100	600	No data	14,000	18,700	No data	18,700
WV	9	72,843	3,456	No data	93,928	170,227	8,403	178,630
WY	2	10,469	No data	No data	26,970	37,439	No data	37,439
Total	119	576,929	56,048	27,699	7,209,933	7,870,609	1,782,654	9,653,263

Source: TRI00 2002

^aData in TRI are maximum amounts released by each facility.^bPost office state abbreviations are used.^cThe sum of fugitive and stack releases are included in releases to air by a given facility.^dThe sum of all releases of the chemical to air, land, water, and underground injection wells.^eTotal amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

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from stationary sources in the United States for 1969–1971, 1978, and 1983 were 900, 1,240, and 1,560 tons selenium/year, respectively (EPA 1974; Lee and Duffield 1979). Dulka and Risby (1976) estimated yearly releases of selenium to the air from fossil fuel combustion to be 1,000 tons. Harr (1978) estimated that 1,500 tons were released annually, with additional air releases from industrial and municipal wastes totaling 2,700 tons and 360 tons, respectively. Selenium releases to the air are likely to increase as more coal is burned in the future. The estimated selenium emissions from Canadian non-ferrous smelters (stack plus fugitive) were 3.02 tons in 1993 (Skeaff and Dubreuil 1997).

Incineration of rubber tires, paper, and municipal waste is an additional source of atmospheric selenium. Hashimoto et al. (1970) reported selenium concentrations in rubber tires to be 1.3 mg/kg. Seventy different kinds of paper have been found to contain selenium (West 1967). Combustion of municipal solid waste results in stack emissions ranging from 0.00098 to 0.00216 pounds (0.44–0.98 g) of selenium per ton of refuse (Johnson 1970).

The amount of selenium contributed to the air by other sources is not known. Microbial action within the soil may also contribute selenium to the air (Fishbein 1983). Selenium biomethylation volatilizes about 3,000 tons of selenium per year into the atmosphere, which eventually returns to earth in rainfall (NAS 1976a). Volcanic gas is suspected to be the major natural source of atmospheric selenium. Certain plants metabolize inorganic selenium compounds to volatile selenium in the forms of dimethyl selenide (Lewis et al. 1971) and dimethyl diselenide (Evans et al. 1968). Animals are also capable of volatilizing selenium and releasing dimethyl selenide in expired air (Schultz and Lewis 1940).

Fly ash settling ponds (which contain high concentrations of selenium) and hazardous waste sites where selenium compounds were disposed of in the past are potential sources of atmospheric selenium through fugitive dust emissions. Selenium emissions from these potential sources have not been quantified.

According to TRI, an estimated total of at least 65,481 pounds of elemental selenium and 576,929 pounds of selenium compounds were discharged to the air from manufacturing and processing facilities in the United States in 2000 (TRI00 2002) (see Tables 6-1 and 6-2). The data listed in the TRI tables should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Selenium has been identified in air at 13 of the 508 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

6.2.2 Water

Surface waters can receive selenium from the atmosphere by dry and wet deposition, from adjoining waters that may contain selenium, from surface runoff, and from subsurface drainage. Sewage treatment plants are another source of selenium releases to water. Effluents from sewage treatment plants and oil refineries appear to be the major sources of selenium in the San Francisco estuarine system (Cutter 1989). In a study of direct discharges from oil refineries in San Francisco Bay, the average selenium concentration in the effluent was 0.067 mg/L with a range of 0.0066–0.156 mg/L (Barceloux 1999; Cutter 1989). Approximately 50–76% of the total selenium in the effluents was selenite. This proportion of selenite is higher than that found in natural estuary sources in the San Francisco Bay (Cutter 1989). About 150,000–460,000 tons of selenium per year are deposited in coal fly ash (Andren and Klein 1975; Doran 1982). Selenium from fly ash settling ponds and hazardous waste sites could reach surface water via runoff or could reach groundwater via leaching. Concentrations of 0.10–0.25 mg/L in a settling basin effluent from coal fly ash in North Carolina were reported by Lemly (1985). Overflow from the ash basin of a coal fired electric generating facility to Belews Lake resulted in surface water selenium concentrations of 0.005–0.020 mg/L in the lake basin. These levels have been reduced considerably since 1986 when the discharge of selenium laden waste water to the lake was discontinued. The peak selenium concentration in 1996 was <0.001 mg/L (Lemly 1997). Selenium concentrations as high as 0.28 mg/L have been reported for raw sewage, 0.045 mg/L for primary effluent, and 0.050 mg/L for secondary effluent (Baird et al. 1972). Irrigation drainage from seleniferous soils can increase selenium concentrations in surface water and has resulted in levels that are toxic to wildfowl at Kesterson National Wildlife Refuge in California (Ohlendorf et al. 1986a, 1988). Selenium was found to be released during coal mining because of the oxidation of selenium-bearing pyrite (Dreher and Finkelman 1992).

According to the TRI, an estimated total of 1,019 pounds of elemental selenium and 56,048 pounds of selenium compounds were discharged to surface water from manufacturing and processing facilities in the United States in 2000 (see Tables 6-1 and 6-2). The data listed in the TRI tables should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Selenium has been identified in groundwater at 271 sites and surface water at 106 sites of the 508 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

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6.2.3 Soil

The primary factor that controls selenium concentrations in soil is the selenium content of the parent bedrock materials that release selenium via weathering processes and leaching (NAS 1976a). Natural weathering processes are thought to release about 100,000–200,000 metric tons of selenium per year (Andren and Klein 1975). Atmospheric deposition of selenium also contributes to selenium in the soil. In the past, selenium was used in pesticide products, but because of its stability in soils and subsequent contamination of food crops, its use in pesticide products is now restricted. The release of selenium to soil from fly ash settling ponds and hazardous waste sites has not been quantified.

According to the TRI, an estimated total of 157,521 pounds of elemental selenium and 7,209,933 pounds of selenium compounds were discharged to land from manufacturing and processing facilities in the United States in 2000 (TRI00 2002). In addition, 40,246 pounds of selenium and 27,699 pounds of selenium compounds were injected underground (see Table 6-2). The data listed in the TRI tables should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Selenium has been identified in soil at 188 sites and sediment at 113 of the 508 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

6.3 ENVIRONMENTAL FATE

The behavior of selenium in the environment is influenced to a large degree by its oxidation state and the consequent differences in the behavior of its different chemical compounds (EPA 1979c; NAS 1976a). The oxidation state of selenium in the environment is dependent on ambient conditions, particularly on pH, pE, and biological activity (Maier et al. 1988).

6.3.1 Transport and Partitioning

The volatile selenium compounds that partition into the atmosphere include the inorganic compounds, selenium dioxide and hydrogen selenide, and the organic compounds, dimethyl selenide and dimethyl diselenide. Hydrogen selenide is highly reactive in air and is rapidly oxidized to elemental selenium and water (NAS 1976a), but the other compounds can persist in air.

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Selenium compounds released to the atmosphere can be removed by dry or wet deposition to soils or to surface water. The annual wet deposition rate of selenium at two rural/agricultural sites in Queenstown, Maryland and St. Mary's, Maryland were 287 and 140 $\mu\text{g}/\text{m}^2\text{-year}$, respectively (Scudlark et al. 1994). Selenium concentrations ranging from 0.04 to 1.4 $\mu\text{g}/\text{L}$ have been detected in rain and snow (Hashimoto and Winchester 1967). Kubota and coworkers (1975) reported selenium concentrations of 0.02–0.37 $\mu\text{g}/\text{L}$ in rainwater at several locations in the United States and Denmark. Selenium was detected at average concentrations of 5.60–7.86 $\mu\text{g}/\text{L}$ during four rainfall events in Riyadh, Saudi Arabia (Alabdula'aly and Khan 2000).

The forms of selenium expected to be found in surface water and the water contained in soils are the salts of selenic and selenious acids. Selenic acid (H_2SeO_4) is a strong acid. The soluble selenate salts of this acid are expected to occur in alkaline waters. Sodium selenate is one of the most mobile selenium compounds in the environment because of its high solubility and inability to adsorb onto soil particles (NAS 1976a). Selenious acid (H_2SeO_3) is a weak acid, and the diselenite ion predominates in waters between pH 3.5 and 9. Most selenites are less soluble in water than the corresponding selenates (NAS 1980b).

Selenium in an aquatic environment is bioaccumulated by aquatic organisms (Chau and Riley 1965; Ohlendorf et al. 1986a; Rudd and Turner 1983a; Saiki and Lowe 1987). Lemly (1985) has reported bioconcentration factors (BCFs) of 150–1,850 and bioaccumulation factors (BAFs) of 1,746–3,975 for selenium in freshwater. In the Kesterson National Wildlife Refuge in the San Joaquin Valley of California, elevated levels of selenium have been measured (dry weight) in algae (average 35 mg/kg), midge larvae (139 mg/kg), dragonfly and damselfly nymphs (average 122 and 175 mg/kg, respectively), and mosquito fish (170 mg/kg) (Ohlendorf et al. 1986b). For comparison, the mean concentrations of selenium found in fish throughout the United States in the 1976–1977, 1978–1979, and 1980–1981 National Pesticide Monitoring Program were 0.56, 0.46, and 0.47 mg/kg wet weight, respectively (Lowe et al. 1985; May and McKinney 1981; Ohlendorf et al. 1986b). Similarly, Lemly (1985) found elevated selenium concentrations in aquatic organisms living in a power plant cooling reservoir in North Carolina. The degree of bioaccumulation of selenium exhibited a stable pattern over several years, with selenium concentrations (wet weight) as follows: fish (6–35 mg/kg) > benthic insects (12–15 mg/kg) > annelids (10–12 mg/kg) > molluscs and crustaceans (5–9 mg/kg) > periphyton (4–6 mg/kg) (Ohlendorf et al. 1986a). In fish, selenium was concentrated in visceral tissue (25–35 mg/kg wet weight) more than in skeletal muscle (6–11 mg/kg wet weight). Adams (1976) reported BCFs of 62.1, 14.3, 6.3, 3.2, and

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10.5 for selenium in the viscera, gill, head and tail, muscle, and whole trout, respectively. The BCFs and BAFs for selenium in visceral tissue (i.e., heart, hepatopancreas, spleen, and gonads) of fish have been estimated to range from 35 to 1,850 and from 1,058 to 3,980, respectively (Lemly 1982, 1985). Lemly (1985) also estimated BAFs for selenium in skeletal muscle of fish to range from 485 to 1,746, depending on the species. Maier et al. (1988) estimated selenium BAFs for algae to range from 100 to 2,600, and Besser et al. (1993) estimated BCFs of 16,000 for algae, 200,000 for daphnids, and 5,000 for bluegills from exposures to 1 µg/L selenomethionine. Selenite was more concentrated than selenate for algae and daphnids, whereas bluegills concentrated both inorganic species about equally (Besser et al. 1993). Selenium accumulation from selenomethionine occurred more readily than from selenite or selenate (Besser et al. 1989).

Some evidence indicates that selenium might biomagnify in aquatic organisms under natural conditions (Lemly 1985; Maier et al. 1988; NCDNR 1986; Sandholm et al. 1973). Biomagnification is evidenced by progressively higher concentrations of an element or substance in organisms at successively higher trophic levels. More than 50% of the selenium contained in sediments in the ponds and the reservoir in the Kesterson National Wildlife Refuge in California occurs in organic forms (Maier et al. 1988), resulting from the synthesis and bioaccumulation of organic selenium before the plants die and decay on the bottom.

In soils, pH and Eh are determining factors in the transport and partitioning of selenium. Elemental selenium is essentially insoluble and may represent a major inert "sink" for selenium introduced into the environment under anaerobic conditions (NAS 1976b). Heavy metal selenides and selenium sulfides, which are also insoluble, predominate in acidic (low pH) soils and in soils with high amounts of organic matter. Selenium in this form is immobile and will remain in the soil. The selenides of other metals such as copper and cadmium are of low solubility (NAS 1976b). Sodium and potassium selenites dominate in neutral, well-drained mineral soils, where some soluble metal selenites may be found as well. In alkaline (pH>7.5), well-oxidized soil environments, selenates are the major selenium species. Because of their high solubility and low tendency to adsorb onto soil particles, the selenates are very mobile (Kabatas-Pendias and Pendias 1984) and are readily taken up by biological systems (Klaassen et al. 1986) or leached through the soil. Gerritse et al. (1982) found selenium to be very mobile in sewage sludge leachate. They reported K_d values (distribution coefficient = [concentration of selenium sorbed on soil or rock]/[concentration of selenium in solution]) of 14.9 mL/g for sandy loam and 5.91 mL/g for sludge-treated sandy soils. Selenite forms stable ferric oxide-selenite adsorption complexes in acid or neutral soils (Geering et al. 1968).

When environments favor the soluble forms of selenium (alkaline and oxidizing conditions), these forms can be accumulated by plants. In addition, although both selenite (Se^{4+}) and selenate (Se^{6+}) are soluble forms of selenium, selenate was found to be the preferred form of selenium taken up by plants (Bañuelos and Meek 1990). Preferential uptake of selenate may be caused by its tendency to be less strongly adsorbed to soil particles and organic matter than selenite (Bañuelos and Meek 1990). Selenium uptake by plants is influenced by many factors including soil type, pH, colloidal content, concentration of organic material, oxidation-reduction potentials in the root-soil environment, and total level of selenium in the soil (Fishbein 1983; Robberecht et al. 1982). In acidic soils (pH 4.5–6.5) and under high moisture conditions, selenium is in the form of selenite and is bound to colloids as iron hydroxide selenium complexes. These complexes are insoluble and generally not bioavailable to plants (Galgan and Frank 1995). In basic soils (pH 7.5–8.5), selenium is present as soluble selenate. Soluble selenates (principally sodium selenate) appear to be responsible for most of the naturally occurring accumulation of high levels of selenium by plants, although much of the total selenium in soil may be present in other forms (NAS 1976a). The use of lime and plant ash as fertilizers, which would raise the pH of the soil and favor the formation of selenate, has been implicated as a contributing factor in the accumulation of selenium in crops grown in high selenium soil found in certain regions of China (Yang et al. 1988).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Selenium dioxide released to the air from the combustion of fossil fuels should be largely reduced to elemental selenium by sulfur dioxide formed during the combustion (NAS 1976b). During a 1991 study, Oehm et al. found that selenium dioxide reacting with atmospheric moisture generates selenious acid aerosols. Hydrogen selenide is unstable in air and is oxidized to elemental selenium and water (NAS 1976a). Hazards from hydrogen selenide are expected, therefore, to be confined to occupational settings where the confined gas might build up to hazardous levels despite oxidative losses (NAS 1976a).

Dimethyl selenide and methyl selenide are volatile organic compounds that can partition into and persist in the atmosphere. Other selenium compounds released to the atmosphere as dust can be removed by wet deposition (in rain or snow) or by dry deposition.

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6.3.2.2 Water

In general, the more soluble and mobile forms of selenium (e.g., selenite and selenate) dominate under aerobic (high oxygen concentrations) and alkaline (high pH) conditions (NAS 1976a; Shamberger 1981). Selenates have been predicted thermodynamically to predominate under aerobic conditions, but a review of the literature indicates that both selenites and selenates are equally common in surface waters (Robberecht and Van Grieken 1982). For selenites in solution, equilibria will be set up between H_2SeO_3 , HSeO_3^- , SeO_3^{2-} , HSe_2O_5^- , and $\text{Se}_2\text{O}_5^{2-}$. The relative concentrations of these species will be determined by the pH of the solution and the total concentration of the electrolytes. Between pH 3.5 and 9, dissolved selenite would be expected to be present predominantly as the diselenite ion, whereas dissolved selenate would occur predominantly as SeO_4^{2-} . Sodium predominates as the counter ion of selenate and selenite in most surface waters.

A study completed by Bender et al. (1991) using a simulated laboratory pond found that bacteria and cyanobacteria have two possible mechanisms for the uptake and transformation of selenate. The uptake mechanism involves the reduction of selenate to elemental selenium that will be physically held within the biological mat. The microorganisms were also found to cause the transformation of soluble selenium into volatile alkyl selenium compounds (Bender et al. 1991).

In some deep aquifers, selenium transport in groundwater was found to be strongly retarded (White et al. 1991). This phenomena is thought to be caused by chemical reduction and precipitation mediated by microbial activity.

Under acidic conditions, selenite can be rapidly reduced to elemental selenium by mild reducing agents such as ascorbic acid or sulfur dioxide (NAS 1980b). Selenate can be converted to selenite or elemental selenium in aquatic systems, but this reaction is slow relative to other transformations. Once formed, elemental selenium is stable over a wide range of pH values and a range of mildly oxidizing to reducing conditions. The formation of various metal selenides is favored by acidic and reducing conditions (NAS 1976b), as found in organic-rich sediments.

Aquatic organisms can convert selenium to both inert and soluble forms. Duckweed, phytoplankton, bacteria, and fungi have been demonstrated to synthesize selenoamino acids from absorbed inorganic selenium compounds (Maier et al. 1988). These selenoamino acids are not likely to be found at significant dissolved concentrations in water, however, because amino acids are rapidly catabolized by

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bacteria. Benthic bacteria and fungi are capable of methylating elemental and inorganic selenium salts (Chau et al. 1976). Hydrogen selenide can be formed in a reducing environment (Cutter 1982; NAS 1976a). Both hydrogen selenide and the methylated forms of selenium are unstable in water and would be expected to rapidly volatilize to the atmosphere (Fishbein 1983).

6.3.2.3 Sediment and Soil

In soils, elemental selenium and inorganic selenium compounds such as sodium selenite can be methylated by microorganisms and subsequently volatilized to the atmosphere (Doran 1982; Fishbein 1983; Shamberger 1981). Microorganisms such as *Aeromonas*, *Flavobacterium*, and *Pseudomonas* are suspected of methylating inorganic and organic selenium compounds to dimethyl selenide and dimethyl diselenide (Doran and Alexander 1976; Fishbein 1983; Reamer and Zoller 1980). Microbes cultured from rhizosphere of bulrush (*Scirpus robustus*) plants were shown to biomethylate soluble selenate and selenite and substantially volatilize these compounds over a 15-day incubation period (Azaizah et al. 1997). Temperature plays a significant role in the microorganism-mediated volatilization of selenium compounds; temperature reductions from 20 to 10 °C and from 20 to 4 °C resulted in 25 and 90% decreases, respectively, in the dimethyl selenide produced (Chau et al. 1976). Reamer and Zoller (1980) examined microbial transformation of selenium in aerobic sewage contaminated with elemental selenium and selenite. They found dimethyl selenide to be the principal microbial product at low selenite concentrations (1–10 mg/kg), whereas dimethyl diselenide and dimethyl selenone were the principal products at higher selenite concentrations (100–1,000 mg/kg). Dimethyl selenide was the only product recovered from sludge contaminated with elemental selenium (Reamer and Zoller 1980). In general, microorganisms appear to methylate organic selenium compounds more readily than either selenite or selenate (Maier et al. 1988). Elemental selenium is converted to methylated selenium compounds the least rapidly (Maier et al. 1988). Selenium methylation and subsequent return from the atmosphere as selenite in rainwater is likely to be the major natural process by which selenium cycling occurs in the environment (Doran 1982).

Demethylation of the trimethylselenonium ion can also occur in soil. Microorganisms are evidently required for this reaction since it did not occur in autoclaved soil (Yamada et al. 1994). Selenium added to the soil as trimethylselenonium was not recovered in the soil, suggesting that trimethylselenonium was demethylated to gaseous selenium compounds, for example, dimethylselenide.

Terrestrial plants take up soluble selenate and selenite and biosynthesize organic selenium compounds, predominantly selenomethionine and, to a lesser extent, selenocysteine. Selenates tend to be taken up by plants from soils more readily than selenites, in part because selenites tend to adsorb more strongly to soils (Dimes et al. 1988; Zhang et al. 1988). These compounds can be released to the soils once the plants die and decay. Water-soluble organic selenium compounds are also probably readily taken up by plants (Shamberger 1981; Shrift 1964).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Selenium can be detected in most biological and nonbiological materials in the environment. Selenium occurs in aquatic and terrestrial organisms as well as in water, air, and soil. Among foods consumed by humans, meat products generally contain the highest concentration of selenium while vegetables and fruits contain the lowest. Brazil nuts contain extremely high levels of selenium since they grow in the foothills of the Andes Mountains, where the soils are high in selenium (Secor and Lisk 1989). Cereals contain intermediate levels of selenium.

6.4.1 Air

Background ambient air concentrations of selenium are generally in the ng/m^3 range (Harrison et al. 1971; John et al. 1973; Peirson et al. 1973). Dams et al. (1970) found concentrations of selenium in suspended air particulate matter of 2.5 ng/m^3 in Niles, Michigan, and 3.8 ng/m^3 in East Chicago, Indiana. During 1968–1969, 18 air samples collected around Buffalo, New York, showed a range of $3.7\text{--}9.7 \text{ ng/m}^3$ (Pillay et al. 1971). Based on these results, the National Academy of Sciences (NAS 1976a) has estimated that the average selenium concentration in the air is well below 10 ng/m^3 . A monitoring study to determine the seasonal variation of pollutants in the air of Alaska was conducted from 1984 to 1987 (Sturges and Shaw 1993). The average concentrations of selenium in Poker Flats, Alaska were 0.035 ng/m^3 (June 1 through January 31, 1984–1987) and 0.067 ng/m^3 (February 1 through May 31, 1984–1987). The nearly 2-fold increase in concentration during the spring months were attributed to local marine biogenic volatilization of selenium, and not a coal burning origin (Sturges and Shaw 1993). Selenium was detected in the ambient atmosphere at seven sites in the United Kingdom at concentrations ranging from 0.1 to 42.3 ng/m^3 (Lee et al. 1994). The lowest levels were observed in the rural areas of Chilton and Windermere with mean concentrations of 1.3 and 0.9 ng/m^3 , respectively. The highest mean concentration of 16.7 ng/m^3 was observed in the industrial area of Walsall.

6.4.2 Water

Selenium has been detected in surface waters and groundwaters in the United States at generally low concentrations. Selenium has been detected in oceans at an average value of 9×10^{-5} mg/L (0.09 µg selenium/L) (Schutz and Turekian 1965). In a study of selenium concentrations in major watersheds of the United States, selenium was detected in only 2 of 535 samples (<0.5%) at a concentration greater than the lowest detection limit of 0.010 mg/L (Lakin and Davidson 1967). Examination of the EPA STORET database for the state of North Carolina revealed that only 3.3% of 657 samples of surface water contained more than 0.001 mg/L, and the highest value was 0.012 mg/L (NCDNR 1986). Watersheds that receive selenium-contaminated waste water have high levels of selenium in surface water samples. The selenium concentration in Lake Belews, North Carolina has dropped from a maximum value of about 0.020 mg/L (pre -1986) to <0.001 mg/L in 1996, due to the discontinued release of selenium laden waste water from a local coal fired power plant (Lemly 1997). The selenium concentration in portions of Pigeon River and Pigeon Lake, Michigan which receive waste water input from a coal fly ash disposal facility, were <0.001–0.0075 mg/L (Besser et al. 1996).

High selenium levels are more likely to be found in irrigation return waters, seeps, springs, and shallow wells where seleniferous soils may contribute to the selenium content of the water. Glover et al. (1979) found that under unusual geological conditions, selenium concentrations in groundwater may reach 0.60 mg/L. In another study conducted in a seleniferous area of South Dakota, 34 of 44 wells did not show any measurable selenium; however, the remaining 10 had concentrations ranging from 0.050 to 0.339 mg/L (Smith and Westfall 1937). Selenium concentrations determined in 107 irrigation and 44 livestock well waters in the San Joaquin area of California exceeded 0.010 mg/L in 26 wells, but exceeded 0.020 mg/L in only 11 wells (Oster et al. 1988a). The maximum concentration was 0.272 mg/L (Oster et al. 1988a).

Selenium accumulation in agricultural drainage waters and basins has been documented in the western United States, particularly in California. The problem was first discovered in the Kesterson Wildlife Refuge in the San Joaquin Valley of California. In 1975, the U.S. Bureau of Reclamation finished construction of an 85-mile subsurface agricultural water drain that terminated in a series of evaporation ponds called Kesterson Reservoir. By 1983, however, it was confirmed that the drain waters contained high concentrations of selenium (>1.35 mg/L in some areas) leached from the soil by application of

irrigation water (Maier et al. 1988). Because the high selenium levels produced death and deformities in fish and waterfowl, delivery of subsurface water to Kesterson was terminated in 1986 (Lewis 1988). Measurements of trace elements in the 27 other evaporation basins in the San Joaquin Valley have revealed only 3 basins with total selenium exceeding 0.10 mg/L and only 50 acres of evaporation basin cells with selenium concentrations in excess of 1.0 mg/L (CRWQCB 1988).

6.4.3 Sediment and Soil

Selenium is estimated to be the 69th most abundant element in the earth's crust, with an average concentration of 0.05–0.09 mg/kg (Glover et al. 1979). Chemically, selenium closely resembles sulfur. Consequently, sulfides of bismuth, iron, mercury, silver, copper, lead, and zinc have been found to contain selenium (Shamberger 1981). Selenium is concentrated in the sulfide minerals galena, chalcopyrite, arsenopyrite, sphalerite, pyrite, marcasite, and pyrrhotite (Coleman and Delevaux 1957). Jarosite and barite have also been found to contain selenium at low levels. The sulfides containing the highest selenium concentrations are those associated with uranium ores in sandstone-type deposits in the western United States. In the immediate vicinity of sandstone-type uranium deposits, selenium concentrations as high as 1,000 mg/kg have been found (Shamberger 1981). Hydrothermal ore is also known to contain high concentrations of selenium. The best known are epithermal gold, silver, antimony, and mercury deposits (Shamberger 1981). Selenium has been found in volcanic rocks in the western United States at concentrations as high as 120 mg/kg (Glover et al. 1979).

Various studies estimated selenium concentration of most soils to be between 0.01 and 0.2 mg/kg (Sindeeva 1964). One study analyzed several thousand soil samples in the United States and found that most seleniferous soils contained <2 mg/kg, with a maximum concentration of <100 mg/kg (Rosenfeld and Beath 1964). The highest U.S. soil levels of selenium are found in areas of the West and Midwest.

Atmospheric deposition of selenium from mining and smelting activities also appears to be a source to soils and plants (Glooschenko and Arafa 1988). In this study, an indirect relationship between distance from smelters and selenium concentration was shown using *Sphagnum fuscum* as an indicator. Washout of atmospheric selenium by precipitation appeared to be the primary mechanism for accumulating selenium in soils and plants in the vicinity of smelters (Glooschenko and Arafa 1988).

Sandstone has been found to contain selenium in varying concentrations, but most probably contains <1 mg/kg (Rosenfeld and Beath 1964). However, sandstone in Wyoming has been found to contain >100 mg/kg (Beath et al. 1946). Generally, the selenium concentration of limestone is low; however, shales of the Niobrara formation in South Dakota have been found to contain over 40 mg/kg. The range of selenium concentrations in phosphate rocks is <1–300 mg/kg (NAS 1976a). Shales appear to contain consistently higher concentrations of selenium than limestone or sandstone. Despite the fact that shales vary so widely in their selenium concentration, they are fairly reliable indicators of soils high in selenium (NAS 1976a).

The disposal of selenium contaminated waste water has resulted in elevated selenium levels in sediments of Lake Belews, North Carolina. The concentration of selenium in sediments ranged from 4 to 12 µg/g (pre-1986), but has dropped to 1–4 µg/g (1996) due to the discontinued release of selenium laden waste water from a local coal fired power plant (Lemly 1997). Selenium was measured in 445 surface soil samples from Florida with a concentration range of 0.01–4.62 µg/g and an arithmetic mean of 0.25 µg/g (Chen et al. 1999). Selenium was detected in soils and bed sediment from the South Platter River Basin at concentrations of 0.30–3.80 µg/g (Heiny and Tate 1997). The highest levels were observed in areas consisting of a high degree of Precambrian rock formation.

6.4.4 Other Environmental Media

Coal and Oil. Petroleum has been found to contain 500–950 mg/kg crude petroleum and 500–1,650 mg/kg heavy petroleum (Hashimoto et al. 1970). An average of 2.8 mg/kg coal has been reported for 138 samples from U.S. deposits (Pillay et al. 1969).

Plants. Several species of grasses and herbaceous plants accumulate selenium, and some of these are endemic to the western United States. Primary accumulators are *Astragalus*, *Oenopsis*, *Stanelya*, *Xylorhiza*, and *Machaeranthera*. Secondary accumulators are *Aster*, *Gutierrezia*, *Atriplex*, *Grindelia*, *Castilleja*, and *Comandra*. Primary accumulators can contain 100–100,000 mg/kg of plant tissue, whereas secondary accumulators contain 25–100 mg/kg of plant tissue (dry weight). Nonaccumulator plants generally contain less than 25 mg of selenium/kg of plant tissue (dry weight) (Rosenfeld and Beath 1964). In some plants, including the leaves of beets and cabbage, and in garlic, as much as 40–50% of the selenium may be in the form of selenate (Cappon 1981).

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A study by Arthur et al. (1992) showed an increased uptake of selenium by terrestrial plants growing on soil-capped fly ash landfill sites. Selenium concentrations rarely exceeded 5 mg/kg, and there were no signs of selenium toxicity to plants. A similar study by Shane et al. (1988) on greenhouse vegetables established that the uptake of selenium by these vegetables is proportional to the percentage of selenium in the growth medium. Another greenhouse study showed that four floating aquatic plants, *Azolla caroliniana*, *Eichjornia crassipes*, *Salvinia rotundifolia*, and *Lemna minor*, absorbed selenium quickly upon exposure (Horne 1991).

Animals. Aquatic animals accumulate selenium from lakes and rivers high in selenium content. Fish in the Kesterson National Wildlife Refuge in California had selenium concentrations up to 96 mg/kg, and aquatic birds had levels up to 130 mg/kg (Barceloux 1999). Selenium was detected in fish from three sites of the Pigeon River and Pigeon Lake in Michigan (Besser et al. 1996). It was determined that selenium concentrations in fish at sites receiving seepage and effluents from a coal fly ash disposal facility were considerably higher than for fish upstream from the facility. Mean concentrations of selenium in white sucker and northern pike ranged from 0.46 to 0.88 µg/g in an uncontaminated portion of the river, while concentrations in a contaminated portion of the river and lake were 1.1–2.4 µg/g (Besser et al. 1996). The mean concentrations of selenium in the feathers of five species of birds at Clear Lake, California were 3.20 µg/g (osprey), 1.38 µg/g (western grebe), 2.51 µg/g (great blue heron), 0.94 µg/g (turkey vulture), and 1.05 µg/g (mallard) (Cahill et al. 1998). Ospreys (which consume large mature fish) had the highest selenium levels, while turkey vultures (which rarely interact with the contaminated aquatic system) and mallards (which are semi-domesticated) had the lowest levels. Selenium was observed in 24 of 24 black-crowned night herons from the Delaware Bay at concentrations of 2.84–5.95 µg/g (Rattner et al. 2000). The highest levels were observed in herons from Pea Patch Island, an island adjacent to a shipping channel for the petrochemical industry. Selenium was observed in the liver of 70 out of 70 redheads (*Athya americana*) in Louisiana and Texas at concentrations of 1.56–5.86 µg/g (Michot et al. 1994). The selenium concentration in moose liver from 12 areas of Sweden ranged from 0.0027 to 3.054 µg/g (Galgan and Frank 1995). The highest levels were observed in areas with a high degree of selenium deposition from industrial sources.

Food. In a review of the foods that contribute the highest proportion of the daily selenium intake of human populations in the United States, Schubert et al. (1987) estimated selenium concentrations in over 100 food items on the basis of 65 articles published after 1960. Table 6-3 presents the selenium concentrations for some of the food items analyzed. The quality of the data was evaluated on the basis of sample size, analytic method, sample handling, sampling plan, and analytic quality control. Schubert et

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**Table 6-3. Selenium Concentrations in Foods in the United States^a
(mg selenium/kg, wet weight)**

Food item	Average	Minimum	Maximum	Number of acceptable samples
Fruits and vegetables				
Apples, raw	0.004	0.003	0.006	5
Carrots, raw	0.017	0.006	0.029	5
Oranges	0.015	0.013	0.018	3
Potatoes	0.013	0.004	0.023	7
Grains, nuts, and cereals				
Bread, white	0.32	0.23	0.54	6
Bread, whole wheat	0.44	0.28	0.67	3
Corn flakes	0.063	0.026	0.12	4
Special K	0.063	0.35	0.94	4
Egg noodles, dry	0.66	0.43	1.35	7
Egg noodles, cooked	0.19	0.14	0.42	2
Nuts, Brazil ^b	14.7	0.20	253	72
Dairy products				
Whole milk	0.016	0.011	0.025	4
Swiss cheese	0.083	0.062	0.10	2
Cottage cheese	0.060	0.052	0.068	2
Meat				
Chicken, cooked	0.21	0.17	0.26	2
Beef, cooked	0.26	0.15	0.52	3
Pork/ham, fresh/cured	0.33	0.19	0.51	6
Salami	0.20	0.13	0.33	2
Seafood ^c				
Salmon, canned	0.75	0.31	1.49	3
Shrimp, canned/cooked	0.64	0.21	1.61	4
Swordfish	2.84	2.54	3.44	4
Organ meats				
Beef liver, cooked	0.56	0.43	0.71	2
Beef kidney, raw	1.70	1.45	2.32	4

^aFood is the normal source of selenium which is essential for human health. Concentrations from Schubert et al. (1987), except where noted.

^bSecor and Lisk (1989)

^cBioavailability of selenium from some fish may be lower than from other foods.

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al. (1987) chose not to present standard deviations or standard errors of the samples because of the different sampling biases present in the studies.

In general, fruits and vegetables were found to contain <0.01 mg/kg, whereas root vegetables contained higher concentrations of selenium (Table 6-3). Beale et al. (1990) found milk and meat to have the same range of selenium concentrations as Schubert et al. (1987). In another study, no apparent correlation existed between the selenium concentration of canned versus fresh fruits and vegetables (Morris and Levander 1970).

Grain products varied greatly in their selenium concentration. Wheat bread and flour were high in selenium, whereas white bread and white flour contained considerably less selenium. Very low levels of selenium were found in certain processed cereals, such as corn flakes, but not in others, such as oat cereal (Morris and Levander 1970; Schubert et al. 1987).

Dairy products contained variable concentrations of selenium as well, but, in general, contained lower levels than meat products. Organ meats (e.g., liver and kidney) and seafoods contained higher levels of selenium than poultry or beef (Morris and Levander 1970; Schubert et al. 1987). The U.S. Fish and Wildlife Service collected 315 whole fish samples from 109 stations nationwide and analyzed them for selenium. Selenium concentrations were as follows (wet weight): geometric mean of $0.42 \mu\text{g/g}$, maximum of $2.3 \mu\text{g/g}$, and 85th percentile concentration of $0.73 \mu\text{g/g}$ (Schmitt and Brumbagh 1990). Consumption of the foods with higher selenium levels contributes to the daily intake of adequate amounts of selenium.

Analysis of commercial baby foods indicated that processing may reduce selenium levels of the food (Morris and Levander 1970).

A recent survey conducted by the U.S. Food and Drug Administration (FDA), which analyzed foods consumed in the United States during the period of 1991–1999, detected selenium in 3,654 out of 6,679 food samples analyzed (FDA 2000). The results of this survey are summarized in Table 6-4.

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Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Overall:		6,671	3,025	1,206	0.07	0.12	0	1.8	0.017
Whole milk, fluid	1	25	5	18	0.019	0.012	0	0.044	0.02
Lowfat (2% fat) milk, fluid	2	25	6	14	0.022	0.015	0	0.056	0.025
Chocolate milk, fluid	3	25	5	15	0.021	0.014	0	0.054	0.023
Skim milk, fluid	4	25	5	14	0.024	0.016	0	0.058	0.025
Plain yogurt, lowfat	6	25	5	9	0.031	0.019	0	0.068	0.033
Chocolate milk shake, fast-food	7	25	5	17	0.023	0.014	0	0.051	0.026
Evaporated milk, canned	8	25	4	4	0.043	0.024	0	0.102	0.047
American, processed cheese	10	25	0	3	0.183	0.025	0.097	0.231	0.178
Cottage cheese, 4% milkfat	11	25	2	4	0.083	0.039	0	0.178	0.08
Cheddar cheese	12	25	0	4	0.198	0.045	0.1	0.318	0.194
Ground beef, pan-cooked	13	25	0	1	0.197	0.052	0.127	0.333	0.187
Beef chuck roast, baked	14	25	0	0	0.251	0.058	0.15	0.379	0.24
Beef steak, loin, pan-cooked	16	25	0	1	0.256	0.063	0.13	0.439	0.24
Ham, baked	17	25	0	1	0.29	0.077	0.12	0.42	0.278
Pork chop, pan-cooked	18	25	0	0	0.46	0.16	0.245	0.808	0.448
Pork sausage, pan-cooked	19	25	0	4	0.215	0.094	0.066	0.556	0.207
Pork bacon, pan-cooked	20	25	0	0	0.38	0.15	0.186	0.836	0.323
Pork roast, baked	21	25	0	1	0.34	0.11	0.13	0.692	0.333

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Lamb chop, pan-cooked	22	25	0	2	0.25	0.13	0.095	0.74	0.22
Chicken, fried (breast, leg, and thigh) homemade	24	25	0	2	0.25	0.1	0.067	0.465	0.243
Turkey breast, roasted	26	25	0	0	0.34	0.14	0.095	0.583	0.329
Liver, beef, fried	27	25	0	0	0.65	0.25	0.089	1.22	0.67
Frankfurters, beef, boiled	28	25	2	3	0.098	0.037	0	0.155	0.102
Bologna, sliced	29	25	0	5	0.134	0.037	0.07	0.239	0.13
Salami, sliced	30	25	0	3	0.202	0.046	0.079	0.313	0.197
Tuna, canned in oil	32	26	0	0	0.69	0.13	0.498	1.013	0.655
Fish sticks, frozen, heated	34	26	0	1	0.168	0.035	0.076	0.257	0.171
Eggs, scrambled	35	26	0	1	0.217	0.073	0.076	0.405	0.206
Eggs, fried	36	25	0	0	0.278	0.084	0.149	0.454	0.259
Eggs, boiled	37	25	0	2	0.27	0.1	0.023	0.477	0.274
Pinto beans, dry boiled	38	25	2	6	0.076	0.043	0	0.13	0.064
Pork and beans, canned	39	25	5	10	0.034	0.023	0	0.076	0.038
Lima beans, immature, frozen, boiled	42	25	17	8	0.005	0.009	0	0.036	0
Green peas, fresh/frozen, boiled	46	25	18	5	0.007	0.013	0	0.044	0
Peanut butter, smooth	47	25	2	8	0.086	0.068	0	0.271	0.073
Peanuts, dry roasted	48	25	5	5	0.075	0.068	0	0.272	0.063

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
White rice, cooked	50	25	3	4	0.057	0.035	0	0.17	0.055
Oatmeal, quick (1–3 minutes), cooked	51	25	2	4	0.058	0.034	0	0.18	0.052
Wheat cereal, farina, quick (1–3 minutes), cooked	52	25	3	3	0.076	0.047	0	0.205	0.069
Corngrits, regular, cooked	53	25	6	13	0.025	0.025	0	0.095	0.019
Corn, fresh/frozen, boiled	54	25	17	6	0.007	0.012	0	0.034	0
Cream style corn, canned	56	25	18	7	0.005	0.008	0	0.029	0
Popcorn, popped in oil	57	26	5	7	0.083	0.071	0	0.267	0.073
White bread	58	25	0	3	0.211	0.075	0.05	0.363	0.197
White roll	59	25	0	0	0.265	0.076	0.144	0.41	0.266
Cornbread, homemade	60	25	1	3	0.124	0.04	0	0.194	0.123
Biscuit, from refrigerated dough, baked	61	24	0	3	0.127	0.038	0.073	0.22	0.119
Whole wheat bread	62	25	0	0	0.32	0.079	0.198	0.48	0.32
Tortilla, flour	63	25	0	1	0.227	0.099	0.032	0.469	0.229
Rye bread	64	25	0	0	0.26	0.061	0.155	0.4	0.246
Blueberry muffin, commercial	65	25	0	3	0.113	0.04	0.065	0.246	0.108
Saltine crackers	66	26	1	5	0.098	0.036	0	0.197	0.1
Corn chips	67	25	5	8	0.04	0.032	0	0.099	0.034
Pancake from mix	68	25	0	5	0.136	0.074	0.05	0.39	0.129

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Egg noodles, boiled	69	25	0	1	0.218	0.082	0.052	0.373	0.232
Macaroni, boiled	70	26	0	1	0.242	0.087	0.034	0.43	0.245
Corn flakes	71	26	5	4	0.057	0.048	0	0.195	0.05
Fruit-flavored, sweetened cereal	72	25	0	5	0.075	0.026	0.031	0.14	0.079
Shredded wheat cereal	73	26	7	5	0.046	0.04	0	0.13	0.044
Raisin bran cereal	74	26	5	9	0.049	0.059	0	0.297	0.035
Crisped rice cereal	75	25	1	10	0.085	0.071	0	0.216	0.044
Granola cereal	76	26	0	2	0.144	0.053	0.066	0.244	0.14
Oat ring cereal	77	26	1	0	0.23	0.078	0	0.335	0.235
Apple, red, raw	78	26	25	1	0	0.002	0	0.011	0
Orange, raw	79	26	24	2	0.001	0.003	0	0.012	0
Banana, raw	80	26	16	8	0.009	0.014	0	0.054	0
Watermelon, raw	81	26	25	1	0	0.002	0	0.012	0
Peach, raw	83	26	25	1	0	0.002	0	0.012	0
Applesauce, bottled	84	26	26	0	0	0	0	0	0
Pear, raw	85	26	26	0	0	0	0	0	0
Strawberries, raw	86	25	23	2	0.001	0.003	0	0.012	0
Fruit cocktail, canned in heavy syrup	87	26	26	0	0	0	0	0	0
Grapes, red/green, seedless, raw	88	26	26	0	0	0	0	0	0
Cantaloupe, raw	89	26	16	10	0.007	0.009	0	0.025	0
Plums, raw	91	26	25	1	0	0.002	0	0.012	0

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Grapefruit, raw	92	26	24	2	0.001	0.003	0	0.011	0
Pineapple, canned in juice	93	26	25	1	0.001	0.003	0	0.017	0
Sweet cherries, raw	94	20	20	0	0	0	0	0	0
Raisins, dried	95	25	24	1	0.001	0.003	0	0.014	0
Prunes, dried	96	25	25	0	0	0	0	0	0
Avocado, raw	97	25	24	1	0.001	0.006	0	0.028	0
Orange juice, from frozen concentrate	98	25	24	2	0.001	0.003	0	0.015	0
Apple juice, bottled	99	25	24	1	0.002	0.008	0	0.04	0
Grapefruit juice, from frozen concentrate	100	26	26	0	0	0	0	0	0
Prune juice, bottled	103	26	25	1	0	0.002	0	0.011	0
Lemonade, from frozen concentrate	105	26	25	0	0.002	0.009	0	0.047	0
Spinach, fresh/frozen, boiled	107	25	18	7	0.003	0.005	0	0.015	0
Collards, fresh/frozen	108	25	17	7	0.005	0.009	0	0.041	0
Iceberg lettuce, raw	109	26	24	2	0.001	0.004	0	0.014	0
Cabbage, fresh, boiled	110	26	21	4	0.003	0.007	0	0.03	0
Coleslaw with dressing, homemade	111	26	17	8	0.011	0.016	0	0.047	0
Sauerkraut, canned	112	26	14	11	0.009	0.015	0	0.071	0

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Broccoli, fresh/frozen, boiled	113	26	16	8	0.011	0.027	0	0.134	0
Celery, raw	114	26	24	2	0.001	0.003	0	0.012	0
Asparagus, fresh/frozen, boiled	115	26	5	11	0.042	0.045	0	0.217	0.034
Cauliflower, fresh/frozen, boiled	116	26	17	7	0.009	0.022	0	0.103	0
Tomato, red, raw	117	25	22	3	0.002	0.005	0	0.019	0
Tomato sauce, plain, bottled	119	26	23	3	0.003	0.008	0	0.037	0
Green beans, fresh/frozen, boiled	121	26	23	3	0.001	0.004	0	0.013	0
Cucumber, raw	123	26	25	1	0	0.002	0	0.011	0
Summer squash, fresh/frozen, boiled	124	26	22	4	0.002	0.005	0	0.019	0
Green pepper, raw	125	26	26	0	0	0	0	0	0
Winter squash, fresh/frozen, baked, mashed	126	26	24	2	0.001	0.003	0	0.012	0
Onion, mature, raw	128	26	18	8	0.006	0.01	0	0.039	0
Radish, raw	132	26	25	1	0	0.002	0	0.011	0
French fries, frozen, heated	134	26	25	1	0.001	0.003	0	0.016	0
Mashed potatoes, from flakes	135	26	21	5	0.004	0.009	0	0.035	0
White potato, boiled without skin	136	26	25	1	0.001	0.005	0	0.028	0

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
White potato, baked with skin	137	26	20	6	0.004	0.007	0	0.02	0
Potato chips	138	26	13	8	0.026	0.046	0	0.217	0.006
Scalloped potatoes, homemade	139	26	14	10	0.012	0.015	0	0.048	0
Sweet potato, fresh, baked	140	26	22	3	0.004	0.009	0	0.033	0
Spaghetti with tomato sauce and meatballs, homemade	142	26	0	4	0.123	0.035	0.048	0.2	0.116
Beef stew with potatoes, carrots, and onion, homemade	143	26	1	5	0.07	0.026	0	0.12	0.071
Macaroni and cheese, from box mix	146	26	0	2	0.195	0.055	0.076	0.339	0.189
Quarter-pound hamburger on bun, fast-food	147	26	0	2	0.177	0.046	0.091	0.3	0.173
Meatloaf, homemade	148	26	0	2	0.191	0.048	0.074	0.3	0.195
Spaghetti with tomato sauce, canned	149	26	0	6	0.106	0.028	0.06	0.187	0.1
Lasagna with meat, homemade	151	26	0	4	0.147	0.032	0.093	0.213	0.147
Chicken potpie, frozen, heated	152	26	3	3	0.071	0.032	0	0.127	0.076

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Chicken noodle soup, canned, condensed, prepared with water	155	26	5	9	0.028	0.018	0	0.06	0.03
Tomato soup, canned, condensed, prepared with water	156	26	22	4	0.002	0.005	0	0.017	0
Vegetable beef soup, canned, condensed, prepared with water	157	26	11	15	0.01	0.01	0	0.026	0.013
White sauce, homemade	160	26	6	6	0.032	0.022	0	0.076	0.035
Dill cucumber pickles	161	26	24	2	0.001	0.004	0	0.017	0
Margarine, stick, regular (salted)	162	25	24	1	0	0.002	0	0.012	0
Butter, regular (salted)	164	26	21	5	0.003	0.007	0	0.021	0
Mayonnaise, regular, bottled	166	26	11	12	0.021	0.021	0	0.078	0.024
Half & half cream	167	26	6	18	0.019	0.013	0	0.042	0.021
Cream substitute, frozen	168	26	26	0	0	0	0	0	0
White sugar, granulated	169	26	26	0	0	0	0	0	0
Pancake syrup	170	26	26	0	0	0	0	0	0
Honey	172	26	26	0	0	0	0	0	0
Tomato catsup	173	26	22	4	0.002	0.005	0	0.016	0

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Chocolate pudding, from instant mix	175	26	6	15	0.027	0.024	0	0.087	0.025
Vanilla flavored light ice cream	177	24	6	10	0.026	0.016	0	0.046	0.03
Chocolate cake with chocolate icing, commercial	178	26	6	11	0.035	0.022	0	0.077	0.041
Yellow cake with white icing, prepared from cake and icing mixes	179	26	7	5	0.035	0.024	0	0.075	0.042
Sweet roll/Danish, commercial	182	26	0	5	0.128	0.04	0.043	0.22	0.123
Chocolate chip cookies, commercial	183	26	6	5	0.043	0.032	0	0.123	0.045
Sandwich cookies with creme filling, commercial	184	26	5	15	0.032	0.022	0	0.081	0.029
Apple pie, fresh/frozen, commercial	185	26	17	9	0.007	0.011	0	0.033	0
Pumpkin pie, fresh/frozen, commercial	186	26	6	11	0.033	0.021	0	0.076	0.037
Milk chocolate candy bar, plain	187	26	4	4	0.046	0.025	0	0.11	0.047
Caramel candy	188	26	10	15	0.017	0.015	0	0.05	0.022
Gelatin dessert, any flavor	190	26	25	1	0.001	0.003	0	0.017	0

6. POTENTIAL FOR HUMAN EXPOSURE

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Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Cola carbonated beverage	191	26	25	1	0.001	0.003	0	0.014	0
Fruit drink, from powder	193	26	25	0	0.001	0.006	0	0.032	0
Low-calorie cola carbonated beverage	194	26	26	0	0	0	0	0	0
Coffee, decaffeinated, from instant	196	26	24	2	0.001	0.006	0	0.032	0
Tea, from tea bag	197	26	25	1	0.001	0.006	0	0.032	0
Beer	198	26	21	5	0.002	0.005	0	0.015	0
Dry table wine	199	26	24	2	0.002	0.008	0	0.04	0
Whiskey	200	26	25	1	0	0.001	0	0.007	0
Tap water	201	26	25	1	0	0	0	0.002	0
Milk-based infant formula, high iron, ready-to-feed	202	25	6	18	0.017	0.011	0	0.03	0.021
Milk-based infant formula, low iron, ready-to-feed	203	25	6	18	0.018	0.011	0	0.037	0.021
Beef, strained/junior	205	26	6	12	0.028	0.02	0	0.075	0.026
Chicken, strained/junior, with/without broth or gravy	207	25	0	1	0.129	0.024	0.063	0.181	0.134

6. POTENTIAL FOR HUMAN EXPOSURE

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Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Chicken/turkey with vegetables, high/lean meat, strained/junior	208	2	0	2	0.064	0.004	0.061	0.066	0.064
Beef with vegetables, high/lean meat, strained/junior	209	2	2	0	0	0	0	0	0
Ham with vegetables, high/lean meat, strained/junior	210	2	0	2	0.102	0.033	0.079	0.125	0.102
Vegetables and beef, strained/junior	211	25	14	11	0.007	0.009	0	0.033	0
Vegetables and chicken, strained/junior	212	26	7	19	0.015	0.015	0	0.073	0.012
Vegetables and ham, strained/junior	213	26	7	18	0.016	0.012	0	0.041	0.018
Chicken noodle dinner, strained/junior	214	26	6	10	0.029	0.018	0	0.064	0.032
Macaroni, tomatoes, and beef, strained/junior	215	26	5	10	0.028	0.017	0	0.06	0.032
Turkey and rice, strained/junior	216	26	7	14	0.025	0.022	0	0.095	0.025

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Carrots, strained/ junior	218	26	25	1	0.001	0.005	0	0.026	0
Green beans, strained/ junior	219	26	24	2	0.001	0.005	0	0.019	0
Mixed vegetables, strained/ junior	220	26	17	7	0.009	0.018	0	0.081	0
Sweet potatoes, strained/ junior	221	26	26	0	0	0	0	0	0
Creamed corn, strained/ junior	222	26	11	9	0.017	0.021	0	0.074	0.012
Peas, strained/ junior	223	26	23	3	0.001	0.004	0	0.016	0
Creamed spinach, strained/ junior	224	25	6	13	0.022	0.017	0	0.068	0.026
Applesauce, strained/ junior	225	26	24	2	0.001	0.003	0	0.012	0
Peaches, strained/ junior	226	26	26	0	0	0	0	0	0
Pears, strained/ junior	227	25	24	1	0	0.002	0	0.012	0
Apple juice, strained	230	25	25	0	0	0	0	0	0
Orange juice, strained	231	26	26	0	0	0	0	0	0
Custard pudding, strained/ junior	232	26	5	10	0.032	0.019	0	0.071	0.035

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Fruit dessert/ pudding, strained/ junior	233	26	25	1	0	0.002	0	0.011	0
Fruit-flavored yogurt, lowfat (fruit mixed in)	235	26	7	14	0.022	0.015	0	0.047	0.024
Swiss cheese	236	26	0	5	0.18	0.054	0.109	0.368	0.174
Cream cheese	237	26	4	8	0.053	0.031	0	0.099	0.054
Veal cutlet, pan-cooked	238	26	0	1	0.165	0.045	0.098	0.354	0.162
Ham luncheon meat, sliced	239	26	0	0	0.237	0.078	0.096	0.374	0.22
Chicken breast, roasted	240	25	0	1	0.27	0.12	0.09	0.623	0.228
Chicken nuggets, fast-food	241	25	0	1	0.2	0.1	0.052	0.595	0.177
Chicken, fried (breast, leg, and thigh), fast-food	242	25	0	1	0.218	0.065	0.131	0.353	0.21
Haddock, pan-cooked	243	19	0	0	0.397	0.076	0.256	0.503	0.4
Shrimp, boiled	244	25	0	0	0.38	0.1	0.2	0.574	0.369
Kidney beans, dry, boiled	245	26	8	12	0.02	0.017	0	0.051	0.019
Peas, mature, dry, boiled	246	26	10	4	0.05	0.09	0	0.457	0.034
Mixed nuts, no peanuts, dry roasted	247	25	1	0	0.53	0.39	0	1.8	0.44
Cracked wheat bread	248	26	0	0	0.285	0.065	0.209	0.448	0.269

6. POTENTIAL FOR HUMAN EXPOSURE

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Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Bagel, plain	249	26	0	0	0.311	0.085	0.165	0.518	0.299
English muffin, plain, toasted	250	26	0	0	0.263	0.068	0.144	0.402	0.25
Graham crackers	251	26	4	3	0.055	0.03	0	0.1	0.057
Butter-type crackers	252	26	4	2	0.061	0.031	0	0.102	0.069
Apricot, raw	253	21	19	2	0.001	0.004	0	0.015	0
Peach, canned in light/medium syrup	254	26	26	0	0	0	0	0	0
Pear, canned in light syrup	255	26	26	0	0	0	0	0	0
Pineapple juice, from frozen concentrate	256	26	26	0	0	0	0	0	0
Grape juice, from frozen concentrate	257	26	26	0	0	0	0	0	0
French fries, fast-food	258	26	22	4	0.003	0.007	0	0.023	0
Carrot, fresh, boiled	259	26	22	4	0.002	0.006	0	0.027	0
Tomato, stewed, canned	260	26	24	2	0.001	0.003	0	0.014	0
Tomato juice, bottled	261	26	20	6	0.004	0.007	0	0.023	0
Beets, fresh/frozen, boiled	262	25	22	3	0.002	0.006	0	0.023	0
Brussels sprouts, fresh/frozen, boiled	263	26	16	8	0.009	0.013	0	0.044	0
Mushrooms, raw	264	26	2	3	0.108	0.054	0	0.227	0.095
Eggplant, fresh, boiled	265	26	26	0	0	0	0	0	0

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Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Turnip, fresh/frozen, boiled	266	26	23	3	0.002	0.006	0	0.025	0
Okra, fresh/frozen, boiled	267	26	22	3	0.003	0.008	0	0.03	0
Mixed vegetables, frozen, boiled	268	26	20	6	0.004	0.008	0	0.032	0
Beef stroganoff, homemade	269	26	0	0	0.191	0.043	0.121	0.311	0.183
Green peppers stuffed with beef and rice, homemade	270	26	3	4	0.065	0.029	0	0.113	0.066
Chili con carne with beans, homemade	271	26	3	6	0.052	0.025	0	0.09	0.057
Tuna noodle casserole, homemade	272	26	0	1	0.173	0.042	0.107	0.281	0.166
Salisbury steak with gravy, potatoes, and vegetable, frozen meal, heated	273	26	6	4	0.034	0.022	0	0.062	0.041
Turkey with gravy, dressing, potatoes, and vegetable, frozen meal, heated	274	26	0	5	0.093	0.025	0.051	0.17	0.091

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Quarter-pound cheese-burger on bun, fast-food	275	26	0	0	0.18	0.041	0.108	0.331	0.18
Fish sandwich on bun, fast-food	276	26	0	0	0.184	0.04	0.109	0.281	0.189
Frankfurter on bun, fast-food	277	26	0	3	0.199	0.048	0.096	0.315	0.197
Egg, cheese, and ham on English muffin, fast-food	278	26	0	0	0.263	0.079	0.095	0.451	0.256
Taco/tostada, from Mexican carry-out	279	26	2	3	0.103	0.039	0	0.161	0.104
Cheese pizza, regular crust, from pizza carry-out	280	26	0	0	0.239	0.053	0.138	0.332	0.235
Cheese and pepperoni pizza, regular crust, from pizza carry-out	281	26	0	0	0.229	0.067	0.068	0.381	0.225
Beef chow mein, from Chinese carry-out	282	26	3	5	0.068	0.043	0	0.192	0.071
Bean with bacon/pork soup, canned, condensed, prepared with water	283	26	7	19	0.015	0.013	0	0.052	0.014

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Mushroom soup, canned, condensed, prepared with whole milk	284	26	5	18	0.021	0.017	0	0.061	0.019
Clam chowder, New England, canned, condensed, prepared with whole milk	285	26	4	12	0.032	0.018	0	0.06	0.036
Vanilla ice cream	286	26	6	19	0.019	0.012	0	0.043	0.021
Fruit flavor sherbet	287	26	21	4	0.005	0.013	0	0.059	0
Popsicle, any flavor	288	26	25	1	0.001	0.006	0	0.03	0
Chocolate snack cake with chocolate icing	289	26	9	15	0.02	0.017	0	0.056	0.025
Cake doughnuts with icing, any flavor, from doughnut store	290	26	0	7	0.097	0.036	0.032	0.164	0.097
Brownies, commercial	291	26	4	7	0.045	0.026	0	0.096	0.049
Sugar cookies, commercial	292	26	4	13	0.039	0.025	0	0.091	0.035
Suckers, any flavor	293	26	24	1	0.003	0.014	0	0.07	0
Pretzels, hard, salted, any shape	294	26	5	7	0.04	0.025	0	0.094	0.043

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Chocolate syrup dessert topping	295	26	20	5	0.006	0.013	0	0.054	0
Jelly, any flavor	296	26	25	1	0.001	0.005	0	0.025	0
Sweet cucumber pickles	297	26	22	4	0.002	0.005	0	0.017	0
Yellow mustard	298	26	0	0	0.33	0.13	0.103	0.724	0.308
Black olives	299	26	25	0	0.001	0.007	0	0.038	0
Sour cream	300	26	4	20	0.027	0.022	0	0.1	0.022
Brown gravy, homemade	301	26	7	9	0.031	0.025	0	0.094	0.032
French salad dressing, regular	302	26	14	10	0.017	0.036	0	0.184	0
Italian salad dressing, low-calorie	303	26	24	2	0.002	0.006	0	0.023	0
Olive/safflower oil	304	26	25	1	0.001	0.003	0	0.014	0
Coffee, from ground	305	26	26	0	0	0	0	0	0
Fruit-flavored carbonated beverage	306	26	25	1	0.001	0.004	0	0.022	0
Fruit drink, canned	307	26	24	2	0.001	0.005	0	0.022	0
Martini	308	26	26	0	0	0	0	0	0
Soy-based infant formula, ready-to-feed	309	26	8	17	0.013	0.009	0	0.023	0.016
Egg yolk, strained/junior	310	12	0	0	0.293	0.026	0.253	0.33	0.292

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-4. U.S. Food and Drug Administration—Total Diet Study (TDS)—Market Baskets 91-3 through 99-1

Selenium—summary of results									
TDS food description	TDS food number	Number of results	Number of not detected	Number of traces	Mean (mg/kg)	Standard deviation (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	Median (mg/kg)
Rice infant cereal, instant, prepared with whole milk	311	26	5	3	0.051	0.03	0	0.093	0.06
Bananas with tapioca, strained/ junior	312	20	9	11	0.011	0.011	0	0.032	0.016
Beets, strained/ junior	313	26	25	1	0	0.002	0	0.01	0
Split peas with vegetables and ham/bacon, strained/ junior	314	15	15	0	0	0	0	0	0
Teething biscuits	316	26	8	18	0.015	0.011	0	0.038	0.017
Rice cereal with apple, strained/ junior	317	26	0	0	0.192	0.052	0.109	0.356	0.188
Squash, strained/ junior	318	6	0	0	0.285	0.052	0.205	0.341	0.29

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Because selenium is ubiquitous in the environment and has been detected in so many media, exposure of the general population to selenium can occur in a variety of ways, including occupational exposure, inhalation, and ingestion of selenium via drinking water, foods, and selenium supplements. For exposure via the food pathway, Schubert et al. (1987) estimated that beef, white bread, pork or ham, chicken, and eggs provide over 50% of the daily selenium intake in the U.S. population. FDA (1982a) estimated that the greatest portion of daily selenium intake occurs from the ingestion of grains and cereals (51.8%). Meat, fish, and poultry were estimated to contribute 36.4% and dairy products were estimated to contribute 9.7% (FDA 1982a).

Various estimates of the selenium intake for Americans have ranged from 0.071 to 0.152 mg/day (DHHS 2002; FDA 1982a; Levander 1987; Pennington et al. 1989; Schrauzer and White 1978; Schubert et al. 1987; Welsh et al. 1981). Schubert et al. (1987) estimated the intake of selenium for the U.S. population to be 0.071 mg/day. They based their estimate on their review of selenium concentrations in different types of foods and the amount of each type of food eaten. The amount of each food type eaten daily was estimated from the U.S. Department of Agriculture's 1977–1978 Nationwide Food Consumption Survey (NFCS). Welsh et al. (1981) estimated the mean daily selenium intake of a group of 22 Maryland residents to be 0.081 mg/day (the median was 0.074 mg/day). In California, the mean daily selenium intake of eight individuals was estimated to be 0.127 mg/day (Schrauzer and White 1978). FDA (1982a) estimated the average daily selenium intake of the U.S. population to be 0.1523 mg/day (152.3 µg/day). Pennington et al. (1989) estimated the daily dietary intake of selenium by age group and by sex between 1982 and 1986, based on FDA's Total Diet Studies for those years, to be between 0.020 mg/day (20 µg/day) for infants and 0.120 mg/day (120 µg/day) for adult males between 25 and 30 years of age. Based on information collected from 1988-94 in the third National Health and Nutrition Examination Survey (NHANES III), the dietary intake of selenium was estimated by sex and age in the United States (see Table 6-5). Based on data from this study, the average dietary intake for all ages and both sexes was estimated to be 0.114 mg/day (DHHS 2002). These values are sufficient to meet the RDA for selenium of 0.055 mg/day for men and women (NAS 2000).

Both inorganic selenium and selenomethionine are found in selenium supplements. The amounts in these supplements generally range from 10 to 25 µg/tablet (Goodman et al. 1990), although current products are

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Table 6-5. Selenium Dietary Intake ($\mu\text{g/day}$) by Sex and Age for the Total U.S. Population, 1988–1994 (DHHS 2002)^a

Sex and age	Sample size	Mean	SEM	Median
Both sexes				
All ages ^b	29,105	114	1.1	99
Under 6 years ^b	6,871	66	0.8	62
6–11 years	3,134	96	1.7	87
12–19 years	3,121	117	2.4	102
20–59 years	10,940	127	1.6	111
60 years and over	5,039	100	1.3	89
Male				
All ages ^b	13,923	134	1.6	118
Under 6 years ^b	3,410	69	1.0	64
6–11 years	1,581	102	2.8	92
12–19 years	1,462	140	3.1	125
20–59 years	5,019	153	2.1	137
60 years and over	2,451	118	1.7	106
Female				
All ages ^b	15,182	94	1.1	85
Under 6 years ^b	3,461	63	0.9	59
6–11 years	1,553	90	1.6	82
12–19 years	1,659	93	2.4	87
20–59 years	5,921	102	1.8	92
60 years and over	2,588	87	1.6	78

^aBased on information collected in the third National Health and Nutrition Examination Survey (NHANES III).^bExcludes nursing infants and children, includes data for poverty income ratio.

SEM = Standard error of the mean

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available in the 100–200 µg/tablet level. A guide to vitamin and minerals recommends that not more than 200 µg selenium/day should be taken in any form (Hendler 1990).

The mean whole blood selenium concentration of residents from 19 U.S. cities ranged from 0.10 to 0.34 mg/L with a mean value of 0.21 mg/L (Barceloux 1999). A synopsis of selenium concentrations in human tissues has been summarized in Table 3-6. Based on information collected from 1988 to 94 in NHANES III, the serum concentration of selenium was estimated by sex and age in the United States (see Table 6-6). Based on data from this study, the mean selenium serum concentration for all ages and both sexes was estimated to be 0.125 mg/L (DHHS 1997).

The National Occupation Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH), estimated that 108,682 workers in 15,127 plants were potentially exposed to selenium in the workplace in 1970 (NOHS 1976). These estimates were derived from observations of the actual use of selenium (1% of total estimate), the use of trade name products known to contain selenium (4%), and the use of generic products suspected of containing the selenium compounds (95%). The largest numbers of exposed workers were heavy equipment mechanics, painters, mechanics in service stations, and special trade contractors. Data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, indicated that 27,208 workers, including 9,632 women, in 1,102 plants were potentially exposed to selenium in the workplace (NIOSH 1983). The majority of these workers were employed in the health services (e.g., nursing), as janitors and cleaners, as machine operators, in the metals industry, or in work involving food and kindred products. These estimates were derived from observations of the actual use of selenium (87% of the total estimate) and the use of trade name products known to contain the selenium compounds (13%) (NIOSH 1989). Neither the NOHS database nor the NOES database contain information on the frequency, level, or duration of the exposure of workers to any of the chemicals listed therein. They are surveys that provide estimates of workers potentially exposed to the chemicals.

The average selenium concentration in the blood of 20 workers employed in a rubber tire repair shop located in Mexico was 148 µg/L, while the average concentration in a control group of 18 healthy volunteers was 100 µg/L (Sánchez-Ocampo et al. 1996). Selenium was measured in the blood of 222 coal miners at concentrations ranging from 34.9–99.5 µg/L (Orszczyn et al. 1996). Selenium content in the blood decreased with age and unexpectedly, smokers had slightly lower blood plasma concentrations than nonsmokers. Furthermore, the most exposed miners (miners exposed to coal dust for more than 10 years)

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Table 6-6. Serum Selenium Concentrations ($\mu\text{g/L}$) in U.S. Population from NHANES III (DHHS 1997)^a

Sex and age	<i>n</i>	Population ^b	Mean	SEM	GM	GM SE
Both sexes						
All ages	18,292	192,615,658	124.75	0.47	123.63	0.44
<6 years old	0	0	—	—	—	—
6–11 years old	0	0	—	—	—	—
12–19 years old	2,968	25,412,279	121.09	0.49	120.03	0.46
20–59 years old	10,519	129,562,302	125.25	0.49	124.17	0.45
60 years and older	4,905	37,641,076	125.48	0.55	124.26	0.54
Males						
All ages	8,561	92,798,087	126.16	0.53	125.10	0.50
<6 years old	0	0	—	—	—	—
6–11 years old	0	0	—	—	—	—
12–19 years old	1,330	12,835,980	121.46	0.58	120.57	0.57
20–59 years old	4,839	63,886,151	127.22	0.56	126.17	0.52
60 years and older	2,392	16,075,956	125.72	0.61	124.54	0.59
Females						
All ages	9,731	99,817,571	123.43	0.45	122.29	0.43
<6 years old	0	0	—	—	—	—
6–11 years old	0	0	—	—	—	—
12–19 years old	1,538	12,576,300	120.71	0.68	119.47	0.63
20–59 years old	5,680	65,676,151	123.34	0.45	122.26	0.42
60 years and older	2,513	21,565,120	125.30	0.58	124.04	0.57

^aData source: Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 (DHHS 1997).
Data analysis: Syracuse Research Corporation, Syracuse, NY, using SUDAAN[®] and SAS[®].

^bPortion of the United States represented by the sample

GM = geometric mean; GM SE = standard error of the geometric mean; SEM = Standard error of the mean

had lower selenium plasma levels than recently hired miners. Although the precise mechanism explaining the decrease in selenium concentration with dust exposure and smoking is unknown, the authors speculated that the decreased selenium levels might reflect its use by the increased demand in antioxidant protection, involving glutathione-peroxidase. Concentrations of selenium in the plasma and urine of copper refinery workers was studied (Rajotte et al. 1996). The levels of selenium in the urine and plasma of the 20 workers were 34.02–189.95 and 113.93–173.57 µg/L, respectively. The respective selenium levels in a control group that was not occupationally exposed were 26.71–118.39 µg/L and 119.51–187.35 µg/L.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are exposed to selenium by the same pathways as adults. The primary route of exposure for children is through the ingestion of food sources. Selenium has been identified in pasteurized milk and milk-based infant formulas in the United States at mean concentrations in the range of 0.011–0.070 mg/kg (Table 6-4). Children may also be exposed to selenium by breast feeding mothers. Selenium was identified in the postpartum breast milk of women at different lactation stages at concentrations of 6.1–53.4 µg/L (Li et al. 1999). Using these concentrations, the daily intake of selenium for fully breast fed infants was estimated to range from 5.2 to 17.9 µg/day. Others have reported the estimated daily dietary intake of selenium for infants as 20 µg/day, while the daily intake for adult males was estimated as 120 µg/day (Pennington 1989). Selenium was detected in the umbilical blood of 350 subjects in the Czech Republic at concentrations of 4.0–82.6 µg/L (Černá et al. 1997). The concentration of selenium in

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the blood of 388 children (196 males, 192 females) ranged from 5.0 to 98.2 µg/L (Černá et al. 1997). Selenium was detected in fetal tissues at a mean concentration of 2.8 µg/g (Robkin et al. 1973). The concentration of selenium in various tissues of infants has been reported by Dickson and Tomlinson (1967) and is summarized in Table 3-6. In areas containing low (0.42 mg/kg), medium (3.09 mg/kg), and high (9.54 mg/kg) seleniferous soils, the mean whole blood selenium levels of school children (7–14 years of age) were 0.13, 0.37, and 1.57 mg/L, respectively (Yang et al. 1989b). Selenium was detected in postmortem liver, lung, and spleen samples of infants in Glasgow, Scotland at mean concentrations of 2.24, 0.76, and 0.099 ppm, respectively (Raie 1996).

The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented. This potential route of exposure is most likely in areas that naturally have high selenium content in soil. Since children often play in fields and soils, both dermal exposure and inhalation of dust particles from soil surfaces are possible. The soluble forms of selenium such as the inorganic alkali selenites and selenates are more likely to be bioavailable in soils than the relatively insoluble selenides. Children are not likely to be exposed to selenium from their parents' work clothes, skin, hair, tools, or other objects removed from the workplace. Selenium is contained in some household products such as shampoos and preparations to treat dandruff and eczema (IARC 1975a). It is also contained in some dietary supplements (Goodman et al. 1990). Since it is unlikely that children would use these products without adult supervision, the potential for overexposure to selenium from these products is low, except for the possibility of accidental poisoning.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Because selenium is a naturally occurring element found in rocks, soils, plants, and animals, the general population is commonly exposed to selenium through diet and drinking water. As a result of the uneven distribution of selenium in the earth's crust, populations living in certain areas of the United States are exposed to greater than average levels of selenium. Areas of the United States with highly seleniferous soils and plants include South Dakota, Wyoming, Montana, North Dakota, Nebraska, Kansas, Colorado, Utah, Arizona, and New Mexico (Valentine et al. 1978). Hawaii also has high levels of selenium in the soil, but not in plants (Smith et al. 1936; Valentine et al. 1978). Human exposure to selenium occurs through the ingestion of food (including meat, milk, eggs, and vegetables) and drinking water from these areas (Smith et al. 1936). Selenium was found at elevated levels in fish from rivers, creeks, and lakes in California, North Carolina, Texas, and Utah (RTI 1993). Farmers and fishermen living in these regions

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may be at higher risk of selenium exposure than people living in urban areas because farmers tend to consume a larger proportion of locally grown foods, and fishermen tend to consume seafood, whereas people in urban areas tend to consume foods grown over a wider geographic area. In addition, people who irrigate their home gardens with groundwater containing high selenium levels may grow and consume plants that contain high levels of selenium because this element accumulates in some plants. Fishermen and hunters of waterfowl who regularly consume fish and game from waterways with elevated selenium levels may increase their selenium body burden, but no reports of selenosis attributable to this practice have appeared in the literature.

People living in the vicinity of hazardous waste sites or coal burning plants may also be exposed to high levels of selenium. Selenosis has been reported in residents of the Wudang Mountains, China where food was grown in highly seleniferous soil (Yang et al. 1989a, 1989b). Selenium blood levels of five patients with long persisting, distinct clinical signs of selenosis ranged from 1.054 to 1.854 mg/L (Yang et al. 1989b). To attain selenium blood levels of this magnitude, it was estimated that the daily intake must be at least 910 µg/day. The mean selenium concentration in hair samples obtained from residents of a highly seleniferous region of Glasgow, Scotland was 18.92 ppm (Raie 1996). By comparison, the mean levels for adults from Iran and Iceland were only 5.72 and 1.81 ppm, respectively.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of selenium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of selenium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of elemental selenium and most of the common environmental forms of selenium have been characterized (Budavari et al. 1996; Lide 2000) and no further data are needed (see Chapter 4).

Production, Import/Export, Use, Release, and Disposal. Knowledge of a chemical's production volume is important because it often correlates with possible environmental contamination and human exposure. Current data regarding the import (USGS 2002), export (USGS 2002), and use (Hoffmann and King 1997) of selenium are available. No statistics regarding the U.S. production of selenium have been reported since 1996 (USGS 2002). Current information on the U.S. production of selenium would assist in identifying potential exposures, particularly in regions of the country where environmental exposure to selenium through food and drinking water is already relatively high.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to EPA. The Toxics Release Inventory (TRI), which contains this information for 2000, became available in May of 2002. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Information is available to permit assessment of the environmental fate and transport of selenium in air (NAS 1976a), water (Chau and Riley 1965; NAS 1980b; Ohlendorf et al. 1986a; Rudd and Turner 1983a; Saiki and Lowe 1987), and soil (Kabatas-Pendias and Pendias 1984, NAS 1976b). Selenium released to the air will be removed by wet and dry deposition. The forms of selenium expected to be found in surface water and the water contained in soils are the salts of selenic and selenious acids. Selenic acid (H_2SeO_4) is a strong acid. The soluble selenate salts of this acid are expected to occur in alkaline waters. Sodium selenate is one of the most mobile selenium compounds in the environment because of its high solubility and inability to adsorb onto soil particles (NAS 1976a). Selenious acid (H_2SeO_3) is a weak acid, and the diselenite ion predominates in waters between pH 3.5 and 9. Most selenites are less soluble in water than the corresponding selenates (NAS 1980b).

It has been suggested that a biological cycle exists for selenium (Shrift 1964), but certain components of the cycle remain uncharacterized. The biological transformation of selenide to elemental selenium has not been well described in the literature (see Maier et al. 1988). Further research on the biological

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selenium cycle might help to identify "hot spots" of selenium in the environment. For example, further investigation of parameters that influence the tendency of selenium to move from one medium to another (e.g., from soil to water) would improve fate and transport modeling efforts.

Bioavailability from Environmental Media. The available monitoring data indicate that selenium is present in samples of air (Dams et al. 1970; Harrison et al. 1971; John et al. 1973; Peirson et al. 1973; Pillay et al. 1971), water (Besser et al. 1996; CRWQCB 1988; Cutter 1989; Glover et al. 1979; Lakin and Davidson 1967; Lewis 1988; Maier et al. 1988; NCDNR 1986; Oster et al. 1988a; Schutz and Turekiam 1965; Smith and Westfall 1937), soil/sediment (Glover et al. 1979; Lemly 1997; Sindeeva 1964), human tissues (Li et al. 1999; Orszczyn et al. 1996; Yang et al. 1989a, 1989b), fish (Besser et al. 1996; Lowe et al. 1985; May and McKinney 1981; Ohlendorf et al. 1986b), and food (Beale et al. 1990; FDA 2000; Schubert et al. 1987). Thus, it can be concluded that selenium is bioavailable from the environmental media.

Food Chain Bioaccumulation. Selenium in food contributed to the highest proportion of the daily selenium intake for human populations in the United States. Fruits, vegetables, milk, meat, and grains contain very low levels of selenium. However, selenium is bioaccumulated by aquatic organisms (Chau and Riley 1965; Ohlendorf et al. 1986a; Rudd and Turner 1983a). Based on reported BCFs and BAFs (Lemly 1982, 1985), selenium is expected to bioaccumulate in fish. Some evidence indicates that under natural conditions, selenium might also biomagnify in aquatic organisms (Lemly 1985; Maier et al. 1988; NCDNR 1986; Sandholm et al. 1973).

Exposure Levels in Environmental Media. Selenium has been detected in air (Dams et al. 1970; Harrison et al. 1971; John et al. 1973; Peirson et al. 1973; Pillay et al. 1971), water (CRWQCB 1988; Cutter 1989; Glover et al. 1979; Lakin and Davidson 1967; Lewis 1988; Maier et al. 1988; NCDNR 1986; Oster et al. 1988a; Schutz and Turekiam 1965; Smith and Westfall 1937), soil and sediment (Beath et al. 1946; Coleman and Delevaux 1957; Glooschenko and Arafat 1988; Glover et al. 1979; Lemly 1997; NAS 1976a; Rosenfeld and Beath 1964; Shamberger 1981; Sindeeva 1964), coal and oil (Hashimoto et al. 1970; Pillay et al. 1969), plants (Arthur et al. 1992; Cappon 1981; Horne 1991; Rosenfeld and Beath 1964; Shane et al. 1988), and food (Beale et al. 1990; FDA 2000; Schubert et al. 1987). Continued monitoring data of selenium levels in the environment are necessary to understand current exposure levels.

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Reliable monitoring data for the levels of selenium and selenium compounds in contaminated media at hazardous waste sites are needed. This information can be used in combination with the known body burden of selenium and selenium compounds to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Selenium has been detected in the blood (Barceloux 1999; Orszczyn et al. 1996), urine (Gromadzinska et al. 1996), hair (Raie 1996; Yang et al. 1989a, 1989b), and nails (Yang et al. 1989a, 1989b) of exposed individuals. Various estimates of selenium intake for the U.S. populations have been reported (FDA 1982a; Levander 1987; Pennington et al. 1989; Schrauzer and White 1978; Schubert et al. 1987; Welsh et al. 1981). The largest numbers of exposed workers were heavy equipment mechanics, painters, mechanics, and special trade contractors (NOHS 1976). Preliminary data from another workplace study indicate that workplace exposure decreased from 1976 to 1984 (NIOSH 1989). Continued monitoring data are necessary to understand and evaluate human exposures to selenium in both occupational and nonoccupational settings.

Exposures of Children. Data are available regarding the exposure and body burdens of children to selenium. Children, like adults, are primarily exposed to selenium through the diet. In areas containing low (0.42 mg/kg), medium (3.09 mg/kg), and high (9.54 mg/kg) seleniferous soils, the mean whole blood selenium levels of school children (7–14 years of age) were 0.13, 0.37, and 1.57 mg/L, respectively (Yang et al. 1989b). Selenium was detected in postmortem liver, lung, and spleen samples of infants in Glasgow, Scotland at mean concentrations of 2.24, 0.76, and 0.099 ppm, respectively (Raie 1996). Children can be exposed to selenium from breast feeding mothers. Selenium was identified in the postpartum breast milk of women at different lactation stages at concentrations of 6.1–53.4 µg/L (Li et al. 1999). Using these concentrations, the daily intake of selenium for fully breast fed infants was estimated to range from 5.2 to 17.9 µg/day. Others have reported the estimated daily dietary intake of selenium for infants as 20 µg/day, while the daily intake for adult males was estimated as 120 µg/day (Pennington 1989). Since selenium is found in soil surfaces and children ingest soil either intentionally through pica or unintentionally through hand-to-mouth activity, pica is a unique exposure pathway for children. While selenium is found in some home products like shampoos (IARC 1975a) and dietary supplements (Goodman et al. 1990), this exposure route should be low and will not disproportionately affect children. Continued monitoring data are necessary to understand potentially dangerous routes of childhood exposure.

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Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for selenium or selenium compounds were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

The development of a registry of exposures would provide a useful reference tool in assessing exposure levels and frequencies. In addition, a registry developed on the basis of exposure sources would allow an assessment of the variations in exposure levels from one source to another and of the effect of geographical, seasonal, or regulatory actions on the level of exposure from a certain source. These assessments, in turn, would provide a better understanding of the needs for research or data acquisition based on the current exposure levels.

6.8.2 Ongoing Studies

A summary of some pertinent ongoing research related to selenium is reported. Federally sponsored research reported in the Federal Research in Progress (FEDRIP 2002) databases is shown in Table 6-7.

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Table 6-7. Ongoing Studies on the Environmental Effects of Selenium^a

Investigator	Affiliation	Study	Sponsor
Finley JW	University of North Dakota (Grand Forks, North Dakota)	Chemical forms of selenium in foods	USDA
Suarez DL, Amrhein C	University of California (Riverside, California)	Selenium and arsenic speciation and mobilization in irrigated soils and drainage waters	USDA
Baligar VC et al.	Virginia Polytechnical Institute and State University, (Blacksburg, Virginia)	Trace elements, chemistry, and plant uptake from soil applied coal by- products/organic amendments	USDA
Reddy KJ	University of Wyoming, (Laramie, Wyoming)	Biogeochemistry and management of salts and potentially toxic trace elements in arid-zone soils, sediments and waters	USDA
Kpomblekou- Ademawou K, Ankumah RO	Tuskegee University, (Tuskegee, Alabama)	Trace elements in broiler littered soils: fate and effects on nitrogen transformation	NRI Competitive Grant
Doner HE	University of California, (Berkeley, California)	Factors controlling the distribution of trace elements in the solid-phase of terrestrial ecosystems	USDA
Terry N	University of California, (Berkeley, California)	Use of constructed wetlands in the bioremediation of selenium contaminated waters	USDA
Basta N	Oklahoma State University (Stillwater, OK)	Chemistry and bioavailability of waste constituents in soils	USDA
Amrhein C	University of California (Riverside, California)	Biogeochemistry and management of salts and possible toxic trace elements in arid soils, sediments and waters	USDA
Doner H, Amundson R	University of California, (Berkeley, California)	Biogeochemistry and management of salts and potentially toxic trace elements in arid-zone soils, sediments and waters	USDA
Dudley LM et al.	Utah State University (Logan, Utah)	Biogeochemistry and Management of salts and potentially toxic elements in arid-zone soils sediments and water	USDA
Logan TJ, Traina, SJ	Ohio State University (Columbus, Ohio)	Chemistry and bioavailability of waste constituents in soils	USDA

^aSource: FEDRIP 2002

NRI = National Research Institute; USDA = United States Department of Agriculture

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring selenium, its metabolites, and other biomarkers of exposure and effect to selenium. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

The analytical methods used to quantify selenium in biological and environmental samples are summarized below. Table 7-1 lists the applicable analytical methods used for determining selenium and selenium compounds in biological fluids and tissues, and Table 7-2 lists the methods used for determining selenium in environmental samples.

7.1 BIOLOGICAL MATERIALS

Sampling of biological material for determination of total selenium concentrations does not usually pose a problem unless specific selenium compounds are to be identified (Bem 1981). One exception is the collection and storage of urine samples without loss of volatile selenium compounds (Bem 1981). Unless special precautions are taken, most analyses of biological materials probably underestimate the concentration of these compounds. Ideally, selenium should be measured in 24-hour urine samples that have been stored in polyethylene containers in acid medium (Sanz Alaejos and Diaz Romero 1993). Blood samples should be separated into plasma or serum and cell fractions prior to freezing if the selenium levels in these components are to be measured separately. Freezing of biological samples immediately following collection is recommended to reduce enzymatic formation of volatile selenium compounds.

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Table 7-1. Analytical Methods for Determining Selenium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (breath)	Calibrate personal sampling pump; sample at a known flow rate for a total sample size of 5–2,000 L; analyze at 190.6 nm	ICP/AES	21 ng/mL	97–105%	NIOSH 1994a (method 7300)
Blood	Mineralize using HNO ₃ -HClO ₄ mixture, generate hydride, and atomize	HGAAS	1x10 ⁻⁸ g/g	No data	Clinton 1977
	Digest blood sample with a nitric/perchloric acid mixture; fume mixture at 200 °C and measure 2,3-diaminonaphthalene	Fluorometric	1.2x10 ⁻⁹ g/g	98%	Rongpu et al. 1986
Blood, plasma, or tissue homogenate	Digest with Mg(NO ₃) ₂ or HNO ₃ at a solution temperature of 100 °C for 60–90 minutes; add HCl; and add hydroxylamine sulfate, EDTA, and urea	GC/ECD	1x10 ⁻⁸ g/g	95–105%	McCarthy et al. 1981
Serum	Dilute sample with matrix modifier containing Mg(NO ₃) ₂ and Ni(NO ₃) ₂ to thermally stabilize Se; heat, dry, atomize; use Zeeman background correction	ZAAS	No data	6.2% relative standard deviation	Lewis et al. 1986b
	Dilute sample with matrix modifier containing NiCl ₂ ; heat, dry, and atomize	GFAAS	No data	84–116%	Oster and Prellwitz 1982
	Nitric-perchloric acid digestion; HCl reduction; sodium borohydride reduction; measure selenium hydride	HGAAS	No data	33–73%	Oster and Prellwitz 1982
	On-line acid ashing of sample followed by hydride generation	ICP/AES	5.5 µg/L	98–106%	Recknagel et al. 1993

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Table 7-1. Analytical Methods for Determining Selenium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	24-hour samples analyzed to measure CT and selenium concentration in urine	Folin-Wu method for CT measurement; fluorimetric method to measure Se	No data	No data	Hojo 1981b, 1982
	Digest sample with HNO ₃ and HClO ₄	Fluorometric	No data	100±22%	Koh and Benson 1983
	Add nitric acid, platinum, and nickel	EAAS	No data	4–8% relative deviation	Saeed 1986
Human spermatozoa and protasomes	Digest with 25% tetramethylammonium hydroxide in methanol	GFAAS	1x10 ⁻⁸ g/g	95.1±5.2%	Suistomaa et al. 1987
Biological samples	Decompose sample with nitric acid; use 1,2-dibromobenzene as a reagent to measure piasselenol	GC/ECD	1x10 ⁻⁹ g/g	No data	Shimoishi 1977
	Spike sample with ⁸² Se; digest; acidify with HCl; react with 4-nitro-o-phenylene-diamine; measure nitro-piasselenol	IDGC/MS	5x10 ⁻¹¹ g/g	No data	Lewis 1988
Liver	Lyophilize sample; irradiate the sample; digest with HNO ₃ , HClO ₄ , and the carrier source; distill sample, and use distillate for analysis	Radiochemical NAA	2.2x10 ⁻¹⁰ g/g	No data	Lievens et al. 1977
Protein (human liver)		INAA and gel filtration	No data	No data	Norheim and Steinnes 1975

CT = creatinine; EAAS = electrothermal atomic absorption spectroscopy; EDTA = ethylenediaminetetraacetic acid; GC/ECD = gas chromatography/electron capture detection; GFAAS = graphite furnace atomic absorption spectroscopy; HCl = hydrochloric acid; HClO₄ = perchloric acid; HGAAS = hydride generation atomic absorption spectroscopy; HNO₃ = nitric acid; ICP/AES = inductively coupled plasma/atomic emission spectroscopy; IDGC/MS = isotope dilution gas chromatography/mass spectrometry; INAA = instrumental neutron activation analysis; Mg(NO₃)₂ = magnesium nitrate; NAA = neutron activation analysis; NiCl₂ = nickel chloride; Se = selenium; ZAAS = graphite furnace atomic absorption spectroscopy with Zeeman background correction

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Table 7-2. Analytical Methods for Determining Selenium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Reduce selenium in sample from SeVI to SeIV; add zinc to the acidified sample; pass gaseous selenium hydride to AA	AA, gaseous hydride	2×10^{-9} g/mL	100%	EPA 1979a (method 270.3)
	Microwave digestion; acidify with HNO_3	ICP-MS	No data	156% (fine flour); 149% (milk powder)	Zhou and Liu (1997)
Water	Acidify sample with HCl, degas solution with N_2 bubbling	HGGC with photo-ionization detection	1×10^{-12} g/mL (0.001 ppb)	No data	Vien and Fry 1988
	Reduce selenium to SeIV with HCl and KBr; coprecipitate with lanthanum hydroxide; centrifuge.	ICP/AES	0.06 $\mu\text{g/L}$	100% selenite; 88% selenate	Adkins et al. 1995
	Acid digestion	ICP/AES	21 ng/mL	97-105%	NIOSH (2001)
Water and waste water	Acid digestion	AA, furnace	2×10^{-9} g/mL	94–112%	EPA 1979a (method 270.2)
Water and wastes	Acid digestion	AA, furnace	5×10^{-9} g/mL	No data	EPA 1984b (method 200.7 CLP-M)
Solid/solid waste/sludge	Aqueous samples subject to acid digestion	AA, furnace	2×10^{-9} g/mL	No data	EPA 1984c (method 7740)
	Acid digestion; measure at 196 nm	ICP and GFAAS	7.5×10^{-8} g/mL	94–112%	EPA 1986c (methods 3050, 6010)
	Acid digestion with HNO_3 /sulfuric acid; convert SeIV to volatile hydride	AA, gaseous hydride	2×10^{-9} g/mL	100%	EPA 1997a (method 7741a)
	Acid digestion	AA, furnace	2×10^{-9} g/mL	No data	EPA 1984b (method 270.2 CLP-M)

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Table 7-2. Analytical Methods for Determining Selenium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Wastes/soil/groundwater	Nitric acid digestion or nitric/peroxide/hydrochloric acid digestion	AA, furnace	3×10^{-9} g/mL	100.5 %	EPA 1997b (method 7742)
Organic waste	Oxidize organic samples, absorb combustion products in NaOH; separate on an ion exchange column	Cathodic stripping	5×10^{-9} g/mL	No data	DOE 1987
Marine biological tissues	Digest aqueous sample with HNO ₃ and perchloric acid Decompose tissue sample with HNO ₃ under pressure; add sulfuric and perchloric acids; heat at 310 °C to evaporate excess acid; add HCl	HGAAS	2×10^{-7} g/g	No data	Welz and Melcher 1985
Marine samples	Digest sample with concentrated HNO ₃ at room temperature; add HNO ₃ , perchloric, and sulfuric acids to complete digestion; evaporate extra acids; dissolve residue in HCl	HGAES-ICP	5×10^{-9} g/mL	No data	DOE 1987
Avian eggs and liver	Digest sample with HNO ₃ ; and hydrogen peroxide to increase solubility	GFAAS	4×10^{-7} g/g	No data	Krynitsky 1987
Fat materials (butter)	Melt butter under an infrared lamp; digest with HNO ₃ , sulfuric, and perchloric acids	HGAAS	10 ppb	No data	Narasaski 1985

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Table 7-2. Analytical Methods for Determining Selenium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plants		Gravimetric method	2×10^{-6} g/g	No data	AOAC 1984 (method 3.101)
	Grind air-dried or fresh samples; acid digest with HNO ₃ and HCl; add EDTA; neutralize with NH ₄ OH; add HCl; shake with decalin; centrifuge decalin layer; read decalin solution with fluorometer at 525 nm within 5 minutes	Fluorometric method	$<4 \times 10^{-6}$ g/g	No data	AOAC 1984 (method 3.102 to 3.107)
Food	Digest sample with HNO ₃ , perchloric, and sulfuric acids; heat; add H ₂ O ₂ ; mix with EDTA, NH ₄ OH, and DAN; boil; add cyclohexane and shake; read cyclohexane layer at 525 nm	Titrimetric method	No data	No data	AOAC 1984 (methods 25.154 and 25.158)
Air (particulate)	Filter particulate matter from air; irradiate and count sample	NAA, non-destructive	1×10^{-10} g/m ³	No data	Dams et al. 1984
Air	Calibrate sampling pump; sample at a known flow rate for a total sample size of 13–2,000 L; analyze at 190.6 nm	ICP/AES	21 ng/mL	97–105%	NIOSH 1994a (method 7300)

AA = atomic absorption; AES = atomic emission spectrometry; CFAAS = graphite furnace atomic absorption spectroscopy; DAN = 2,3-diaminonaphthalene; EDTA = ethylenediamine tetraacetate; HCl = hydrochloric acid; HGAAS = hydride generation atomic absorption spectroscopy; HGAES = hydride generation atomic emission spectroscopy; HGGC = hydride generation gas chromatography; HNO₃ = nitric acid; ICP = inductively coupled plasma; KBr = potassium bromide; N₂ = nitrogen; NAA = neutron activation analysis; NaOH = sodium hydroxide; NH₄OH = ammonium hydroxide

A variety of analytical methods can be used to determine trace concentrations (ng/g) of selenium in biological tissues. These include fluorometry, neutron activation analysis (NAA), atomic absorption spectroscopy (AAS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), gas chromatography (GC), spectrophotometry, x-ray fluorescence analysis, and others.

Classical flame AAS techniques do not have sufficiently low detection limits for selenium to be useful for determining its presence in biological samples (Koirttyohann and Morris 1986). Hydride generation atomic absorption spectroscopy (HGAAS) has been used instead for determination of selenium in biological samples such as blood and blood constituents and meat, fruits, and vegetables (Bem 1981).

Graphite furnace atomic absorption spectroscopy (GFAAS) offers high sensitivity (5×10^{-11} g selenium/g sample), but interference from the matrix can cause significant difficulties (Lewis 1988). GFAAS methods rely on the fact that numerous metal compounds react with selenium compounds to form relatively refractory metal selenides (Oster and Prellwitz 1982). Nickel, molybdenum, and platinum are commonly added to the sample to thermally stabilize the selenium. Organic materials are then destroyed by high temperature in the furnace prior to atomization of the sample at very high temperatures (e.g., 2,700 °C) (Oster and Prellwitz 1982). One advantage of GFAAS techniques is that the material in the graphite sample cell can be chemically treated *in situ* to reduce chemical interference. GFAAS techniques require correction for background absorption. Correction techniques include the deuterium continuum light source method (Hoenig and Van Hoeyweghen 1986) and the Zeeman splitting of the absorption line (Koirttyohann and Morris 1986). A Zeeman-effect system, which applies a magnetic field to the atomizer, allows the background correction to be performed at the exact analyte wavelength without the use of auxiliary light sources (Fernandez and Giddings 1982). The Zeeman-effect background correction is necessary for the determination of selenium in blood and blood products when GFAAS is used because a spectral interference from iron occurs at the selenium wavelength that cannot be corrected by a deuterium continuum source.

A modification of the GFAAS method for determining selenium levels in human urine was described by Saeed (1986). In this electrothermal atomic absorption spectrometry (EAAS) method, nitric acid, nickel, and platinum are added to the graphite cell. The addition of nickel helps to mask the spectral interference from phosphates in urine. EAAS has been used to determine selenium levels in human spermatozoa (Suistomaa et al. 1987). For human blood plasma and serum, the detection limit of the EAAS method

was 0.8 µg/L (2 ng absolute), with recoveries of 87–96% for plasma and 94–104% for serum (Harrison et al. 1996).

HGAAS offers reduced chemical interference but requires larger sample volumes than GFAAS techniques (Koirtyohann and Morris 1986). HGAAS techniques have been used to measure selenium concentrations in food (Fiorino et al. 1976). These techniques use wet-sample digestion (e.g., nitric-perchloric acid) to destroy organic matter. Sample reduction to convert Se(VI) (+6 valence state) to Se(IV) (+4 valence state) is necessary prior to using sodium borohydride to reduce all selenium present to selenium hydride (Macpherson et al. 1988). The selenium hydride is thermally decomposed and atomized in the sample beam of the atomic absorption spectrophotometer. Nitric-perchloric acid is commonly used for the digestion step. Because perchloric acid is potentially explosive, use of phosphoric acid instead is also common. Following the International Union of Pure and Applied Chemists (IUPAC) interlaboratory trial for the determination of selenium in human body fluids, Welz and Verlinden (1986) reported that it was important to use a temperature of at least 200 °C for sample decomposition when using HGAAS. They attributed the severe imprecision and systematic errors in measuring selenium in multiple samples to improper sample decomposition. Norheim and Haugen (1986) demonstrated that a combined system of a wet digestion and an automated hydride generator could analyze approximately 80 samples per day.

ICP-AES with hydride vapor generation has been used to determine total selenium in biological samples (Tracy and Moller 1990). This technique is especially suited to the analysis of small samples. Samples are wet ashed with nitric, sulfuric, and perchloric acids at temperatures up to 310 °C. After treatment with hydrochloric acid, selenium is reduced by sodium borohydride to hydrogen selenide in a simplified continuous flow manifold. A standard pneumatic nebulizer affects the gas-liquid separation of H₂Se, which is quantified by ICP-AES at 196.090 nm. The instrument detection limit for this method has been determined to be 0.4 µg/L

Hydride generation atomic fluorescence spectrometry (HGAFS) has been used to measure selenium concentrations in urine (Sabé et al. 2001). Samples were completely mineralized using a focused microwave oven with a mixture of nitric acid and sulfuric acid for 14 minutes. Complete recovery was achieved from selenocystine (SeCys), selenomethionine (SeMet), and trimethyl selenium (TMeSe) species. The detection and limit of quantization for this method were 57 and 190 pg selenium/L.

Application of gas-liquid chromatography (GLC) to determine selenium in biological samples allows for the elimination of interference from the biological matrix. GLC requires prior decomposition of organic

matter with nitric acid. GLC techniques are based on measurement of the amount of piaszelenol formed by the reaction of selenium (*IV*) with appropriate reagents in acidic media (Bem 1981). For gas chromatographic determination of selenium with an electron capture detector, 1,2-diaminoarenes can be used as reagents to produce piaszelenols (McCarthy et al. 1981; Poole et al. 1977; Shimoishi 1977; Young and Christian 1973). Using 1,2-diamino-3,5-dibromobenzene as a reagent, Shimoishi (1977) obtained a detection limit of 1×10^{-9} g selenium per gram of sample.

Isotope dilution gas chromatography/mass spectrometry (IDGC/MS) is a highly accurate technique that is more accessible than NAA techniques. IDGC/MS has been used to determine selenium in foods, plasma and serum, red blood cells, feces, urine, and human breast milk (Lewis 1988). The minimum sample size per determination is 0.5–10 g (0.5–10 mL). In the IDGC/MS method, a stable selenium isotope is added to the sample prior to digestion. This procedure eliminates the need for quantitative sample preparation and external standardization (Lewis 1988). However, a disadvantage of this technique is that enriched isotopic standards are expensive.

NAA techniques provide lower detection limits for selenium (between 10^{-8} and 10^{-9} g selenium per gram of sample), but there are few reactors at which NAA facilities and expertise are available (Koirtyohann and Morris 1986). The most common NAA procedure for selenium determination is to produce the long-lived ^{75}Se radionuclide (half-life of 119 days) and count the samples after a 50–100-hour irradiation period and a 2–10-week cooling period. A faster NAA technique utilizes metastable $^{77\text{m}}\text{Se}$, which has a much shorter half-life (17.4 seconds), so that counting can be initiated after an irradiation and cooling period of <1 minute (Koirtyohann and Morris 1986). The most common standard reference sample for NAA techniques is bovine liver tissue (Bem 1981). Biological tissues that can be analyzed for selenium using the NAA technique include bone, hair, liver, kidney, lung, serum, blood, feces, urine, brain, stomach, skin, aorta, heart, testis, pituitary gland, tooth enamel, tongue, muscle, spleen, and thyroid (Yukawa et al. 1980). For many NAA techniques, destructive sample pretreatment (involving radiochemical separation) is required to avoid interference from the biological matrix (Koirtyohann and Morris 1986). The advantages of NAA are its low detection limits and multielement capability (Molokhia et al. 1979). Because facilities at which NAA can be performed are extremely limited, NAA's most useful application is as a reference method against which other less expensive and more common methods can be compared for accuracy.

Spectrophotometric, fluorometric, voltammetric, and x-ray fluorescence analysis methods have also been successfully employed to determine selenium levels in blood, tissue, and human hair. Of these,

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fluorometric methods are most commonly used (Koh and Benson 1983). The reaction of selenium(VI) with 2,3-diaminonaphthalene (DAN) or with 3,3-diaminobenzidine (DAB) to form a fluorescent Se-DAN or Se-DAB heterocyclic compound is the basis of the fluorometric method of selenium determination (Allaway and Cary 1964; Chen et al. 1982; Lewis 1988). The piarselenol formed with DAN as the reagent has greater fluorescence sensitivity than the piarselenol formed with DAB as the reagent and is also extractable into organic solvents from acid solution (Chen et al. 1982). Fluorometric techniques require sample digestion to destroy organic matter and sample reduction to convert the selenium to the selenium(IV) oxidation state (Macpherson et al. 1988). Loss of volatile selenium compounds is possible during sample digestion and manipulation because several steps are required. Chen et al. (1982), Hasunuma et al. (1982), and Koh and Benson (1983) developed modifications of the digestion and treatment steps for selenium determination by fluorometric methods. Their methods allow small sample sizes, can be performed in a single flask, and measure submicrogram amounts of selenium.

Some of the methods for determining selenium in biological materials have been compared within the same laboratory for accuracy and precision. Macpherson et al. (1988) compared the accuracy of three methods for the determination of selenium in biological fluid samples from biological materials with certified selenium levels. Acid decomposition fluorometry, HGAAS, and EAAS gave equally accurate results. Lewis et al. (1986) compared the graphite furnace atomic absorption spectrometry with the Zeeman-effect background correction (ZAAS) to isotope dilution mass spectrometry (IDMS) for determination of selenium in plasma and concluded that the ZAAS method compared favorably (correlation coefficient 0.987), but was half as precise as the IDMS method. Oster and Prellwitz (1982) compared HGAAS and GFAAS for the determination of selenium in serum. They concluded that the two techniques exhibited approximately equal detection limits in their laboratory.

In three studies that compared analytical methods for the detection of selenium in biological samples, all found that fluorometry gave both accurate and reliable results (Burguera et al. 1990; Heydorn and Griepink 1990; Macpherson et al. 1988). Burguera et al. (1990) indicated the acceptance of HGAAS as yielding reliable results, whereas Heydorn and Griepink (1990) reported HGAAS had a high relative standard deviation of 11.4%.

Decomposition procedures have been improved and analytical methods have been modified in recent years to increase the accuracy and speed of determination of selenium concentrations in plasma, serum, and urine. Reamer and Veillon (1983) used phosphoric acid along with nitric acid and hydrogen peroxide in digestion of biological fluids instead of perchloric acid to prepare samples for fluorometry. They

concluded that phosphoric acid digestion increases the safety and convenience of the determination. Krynitsky (1987) used a modified wet digestion method for the determination of selenium in biological samples such as eggs and liver of avian species. This method uses hydrogen peroxide to enhance the solubility of the sample. Digestion with HNO_3 and HClO_4 is essential for accurate analysis of the total selenium in urine to ensure complete oxidation of the trimethylselenonium ion (Koh and Benson 1983).

7.2 ENVIRONMENTAL SAMPLES

Many of the basic analytical methods used for determining selenium in biological media are also used for determining selenium levels in soil, water, and air. Precautions in the collection and storage of environmental samples, however, are necessary to prevent loss of the volatile selenium compounds to the air. The destruction of organic matter before selenium measurement is also often necessary. Acidification of water samples to a pH of 1.5 is recommended to preserve selenium compounds (Muñoz Olivas et al. 1994). Nitric acid can be used, although it interferes with the hydride generation method of analysis. The best storage method for selenium compounds in water is in glass containers at 4 °C (Wiedmeyer and May 1993).

The analytic methods generally fall into two groups: (1) those that do not require the destruction of organic materials in the sample and (2) those that require the elimination of interfering matter before the selenium content can be measured. X-ray fluorescence and some of the neutron activation analysis techniques do not require sample destruction, whereas spectrophotometry, GC, atomic absorption spectrometry, polarography, titration, spark source, MS, fluorometry, and other neutron activation analysis techniques require some degree of sample destruction. Fluorometry, atomic absorption spectrometry, and neutron activation analysis are the most frequently used methods.

Inductively coupled plasma (ICP) emission techniques can be used to measure selenium concentrations. ICP techniques offer multielement capabilities, but instrumentation is costly and background interference can be a problem (Koirtzohann and Morris 1986). The NIOSH-recommended method for determining selenium in air is inductively coupled argon plasma atomic emission spectroscopy (NIOSH 1994a). Selenium may be measured in water following NIOSH Method 7300. The limit of detection for this method is 21 ng/mL using a selenium emission line at 190.6 nm (NIOSH 2001). ICP-MS has been used to determine the concentration of selenium in cloud water at detection limits of 100 and 25 pg/mL using pneumatic and ultrasonic nebulization, respectively (Richter et al. 1998).

AAS techniques are commonly used for the determination of selenium in environmental samples. Hydride generation AAS is more sensitive than flame or graphite furnace AAS for the determination of selenium in materials of variable composition. Water samples, including freshwater, river water, sea water, and surface waters, and industrial wastes, muds, sediments, and soil samples have been analyzed by AAS techniques to detect selenium at parts-per-trillion levels (Bem 1981). Selenium(VI) and selenium(IV) can be distinguished in water samples with GFAAS by selective extraction procedures. HGAAS can also be used to distinguish between selenium(VI) and selenium(IV) in environmental samples because selenium(VI) does not readily form the hydride without reduction (Koirtzohann and Morris 1986). Selenium(VI) is calculated on the basis of the total selenium minus selenium(IV) (Bem 1981).

NAA has been used to determine selenium levels in environmental samples. Dams et al. (1970) reported a detection limit of 1×10^{-10} g/m³ selenium using nondestructive NAA for determining selenium in air particulate matter. For determining selenium levels in soil, radiochemical variants of NAA have been commonly employed (Bem 1981). Instrumental neutron activation analysis (INAA) is frequently used to determine selenium concentrations in water and can also be used to distinguish between selenium(IV) and selenium(VI) oxidation states (Bem 1981). INAA is also used to determine selenium concentrations in air (Bem 1981).

Gas liquid chromatography allows for elimination of interference from the matrix when analyzing environmental samples. When analyzing biological samples, a variety of reagents can be used to convert selenium to piasselenols for measurement with an electron capture detector. Spectrophotometric determinations of selenium are performed using organic reagents, whereas fluorometric analysis relies on piasselenol fluorescence to measure submicrogram levels of the element.

The hydride generation GC with photoionization detection (HGGC-PD) method for selenium determination was developed by Vien and Fry (1988). The combined usage of a photoionization detector and a cold trap provided at least two orders of magnitude improvement in detectability over the existing GC systems. The detection limit for the HGGC-PD method was 1×10^{-12} g selenium/mL (0.001 ppb) for 28 mL samples. An advantage of the HGGC-PD technique is the ability to perform simultaneous determinations of at least four different hydride-forming elements (Vien and Fry 1988).

EPA's Contract Laboratory Program (EPA 1984b) requires the participating laboratories to meet the Contract Required Detection Level (CRDL) for selenium of 5×10^{-9} g selenium/mL (5 µg selenium/L) using proven instruments and approved analytical techniques, including ICP and atomic absorption methods.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of selenium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of selenium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods that distinguish among the various selenium compounds are not commonly used to estimate human exposure to selenium, but have been used in specialized metabolic studies. Analytical methods currently used to measure concentrations of selenium in biological fluids or human tissue samples as an indication of human exposure are described in Table 7-1. Attempts to use measures of whole blood GPX activity levels as indicators of human exposure to selenium have not been successful. Errors can result if the selenium-dependent GPX activity is not distinguished from the nonselenium-dependent GPX activity (Edwards and Blackburn 1986). In addition, whole blood selenium concentrations and GPX activity appear to correlate with one another only at low blood selenium levels (<0.100 mg selenium/L) (Allaway et al. 1968; Valentine et al. 1980). GPX activity levels measured in

platelets have provided an indication of selenium exposure levels at low blood selenium levels (Nève et al. 1988). Whether platelet GPX activity levels would provide an indication of selenium status in populations with plasma selenium levels above 0.012 mg selenium/L is not known. There is great variability in the exposure data available for humans. Therefore, until larger databases of selenium concentrations in biological materials from affected and unaffected populations are available, no recommendations for analytical methods can be made.

Effect. There are no known sensitive and specific biomarkers of effect for selenium. Therefore, no analytical methods recommendations can be made for biomarkers of effect for selenium, at the present time.

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Numerous analytical methods are available for the determination of selenium levels in environmental media (AOAC 1984; Bem 1981; Dams et al. 1970; DOE 1987; EPA 1984b, 1986c; Koirtiyohann and Morris 1986; NIOSH 1994a; Vien and Fry 1988). However, most of these do not distinguish among the various selenium compounds. Many of the available methods can be used to detect selenium at subnanogram levels. For the determination of selenium only, fluorometry, chromatography, or spectrometry are the preferred techniques. When conducting a multielemental analysis or when analyzing a complex matrix, more sophisticated methods are required.

It is possible to detect selenium levels as low as 1 ng/m³ of air using neutron activation analysis. Standardized methods for selenium determination in different environmental samples such as water, soil, sludge, and industrial waste are available in the above-mentioned literature.

There are fewer methods available for distinguishing among the inorganic forms of selenium in the environment. HGAAS, INAA, and GFAAS with selective extraction procedures can be used to distinguish between selenium(VI) and selenium(IV) in samples of soil and water. Methods for determining selenium sulfide levels in the environment are lacking, but would be useful for the identification and measurement of this potentially carcinogenic selenium compound.

Very limited information is available regarding the sensitivity, reliability, and specificity of the existing methods. Further studies to determine these factors would be useful.

7.3.2 Ongoing Studies

N.J. Miller-Ihli and coworkers at the Agricultural Research Service (Beltsville, Maryland) are conducting studies to develop single and multielement methods for the determination of trace elements of nutritional and health concern (e.g., selenium). Some techniques proposed in their studies include: GFAAS and electrothermal vaporization inductively coupled plasma-mass spectrometry (ICP-MS); inductively coupled plasma-atomic emission spectrometry (ICP-AES); electrothermal vaporization ICP-MS (USS-ETV-ICP-MS) and USS-GFAAS; and capillary zone electrophoresis (CZE) coupled with ICP-MS (FEDRIP 2002).

8. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for selenium by various national and state agencies. These values are summarized in Table 8-1.

The current Recommended Dietary Allowances (RDAs) for selenium, established by the Food and Nutrition Board of the National Research Council (National Academy of Sciences) (NAS 2000), are listed below. The recommended Tolerable Upper Intake Level (UL) for selenium in adults is 0.4 mg/day (NAS 2000). The UL is defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population.

Men: 0.055 mg/day

Women: 0.055 mg/day

Pregnant women: 0.060 mg/day

Lactating women: 0.070 mg/day

Infants (0–6 months): 0.015 mg/day

Infants (7–12 months): 0.020 mg/day

Children (1–3 years): 0.020 mg/day

Children (4–8 years): 0.030 mg/day

Children (9–18 years): 0.040 mg/day

A chronic oral MRL of 0.005 mg/kg/day was derived for selenium based on a NOAEL of 0.015 mg/kg/day for disappearance of symptoms of selenosis in recovering individuals (Yang and Zhou 1994), as discussed in Section 2.3. The NOAEL was divided by an uncertainty factor of three to account for sensitive individuals. The EPA used the same human NOAEL for clinical selenosis (0.015 mg/kg/day) (Yang et al. 1989a, 1989b) and an uncertainty factor of three to derive a chronic oral reference dose (RfD) of 0.005 mg/kg/day for selenium (EPA 2003).

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3 ^a	IARC 2001
WHO	Guideline for drinking water Recommended daily intake for adults	0.01 mg/L 0.9 µg/kg body weight	WHO 2001
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA) Selenium and compounds Selenium hexafluoride	0.2 mg/m ³ 0.16 mg/m ³	ACGIH 2000
EPA	Hazard rank under Section 112(g) of the Clean Air Act Amendments Reference air concentration	42 out of 1–100, with 100 being the most toxic 3.0 µg/m ³	EPA 2001a EPA 2001b 40CFR 266, Appendix IV
NIOSH	REL (TWA) Selenium and compounds, except selenium hexafluoride	0.2 mg/m ³	NIOSH 2001
OSHA	IDLH Selenium and compounds General industry PEL (TWA) Selenium and compounds Selenium hexafluoride Hydrogen selenide Construction industry PEL (TWA) Selenium and compounds Selenium hexafluoride	1.0 mg/m ³ 0.2 mg/m ³ 0.4 mg/m ³ 0.2 mg/m ³ 0.2 mg/m ³ 0.16 mg/m ³	OSHA 2001 29CFR1910.1000, Table Z OSHA 2001
b. Water			
EPA	MCLG	0.05 mg/L	EPA 2001c 40CFR141.51
	MCL	0.05 mg/L	EPA 2001d 40CFR141.62
	DWEL	0.2 mg/L	EPA 2000
	Health advisory—lifetime Groundwater monitoring (PQL)	0.05 mg/L 750 µg/L	EPA 2001e 40CFR264, Appendix IX
	Groundwater monitoring—concentration limits	0.01 mg/L	EPA 2001f 40CFR264.94

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>NATIONAL</u> (cont.)			
EPA	Water quality standards		EPA 2001g
	Freshwater		40CFR131.36
	Maximum concentration	20 µg/L	
	Continuous concentration	5.0 µg/L	
	Saltwater		
	Maximum concentration	290 µg/L	
c. Food FDA	Continuous concentration	71 µg/L	
	Approved use of selenium as a food additive in animal feeds—added to feed for chickens, swine, turkeys, sheep, cattle, and ducks	≤0.3 ppm	FDA 2001a 21CFR573.920
	Bottled water—allowable level	0.05 mg/L	FDA 2001b 21CFR165.110
	RDA (mg/day)		NAS 2000
	Men	0.055	
	Women	0.055	
	Pregnant women	0.060	
	Lactating women	0.070	
	Infants (0–6 months)	0.015	
	Infants (7–12 months)	0.020	
	Children (1–3 years)	0.020	
	Children (4–8 years)	0.030	
	Children (9–18 years)	0.040	
d. Other EPA	Carcinogenicity classification		IRIS 2001
	Selenium and compounds	Group D ^b	
	Selenium sulfide	Group B2 ^c	
	Designation of hazardous substances		EPA 2001h 40CFR116.4
	Selenium oxide		
	Sodium selenite		
	Determination of reportable quantities		EPA 2001i 40CFR117.3
	Selenium oxide	10 pounds	
	Sodium selenite	100 pounds	
	Extremely hazardous substance		EPA 2001j 40CFR355, Appendix B
	Reportable quantity		
	Hydrogen selenide	10 pounds	
	Selenious acid	10 pounds	
	Selenium oxychloride	500 pounds	
	Threshold planning quantity		
	Hydrogen selenide	10 pounds	
	Selenious acid	1,000/10,000 pounds	
	Selenium oxychloride	500 pounds	

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
NATIONAL (cont.)			
EPA	Identification and listing of hazardous waste		EPA 2001k 40CFR261, Appendix VIII
	Selenium		
	Selenium and compounds		
	Selenium dioxide		
	Selenium sulfide		
	Selenium tetrakis, (dimethyl-dithiocarbamate)		
	Selenious acid		
	Selenourea		
	Thallium selenite		
	Protection standards at inactive uranium processing sites—listed constituents		EPA 2001l 40CFR192, Appendix I
	Selenium and compounds		
	Selenium dioxide		
	Selenium sulfide		
	Recommended daily allowances		EPA 2001m
	Selenium and compounds		
	Men	0.7×10^{-1} mg/kg/day	
	Women	0.55×10^{-1} mg/kg/day	
	Infants	8.7×10^{-4} mg/kg/day	
	Reportable quantity		EPA 2001n 40CFR302.4, Appendix A
	Selenium and compounds	1 pound	
	Selenium dioxide	1,000 pounds	
	Selenium sulfide	1 pound	
	Selenious acid	1 pound	
	Selenourea	1 pound	
	Sodium selenite	1,000 pounds	
	Thallium selenite	1 pound	
	Reportable quantity		EPA 2001o 40CFR117.3
	Selenium oxide	10 pounds	
	Sewer sludge—disposal or use standards		EPA 2001p 40CFR503.13
	Ceiling concentration	100 mg/kg	
	Cumulative pollutant loading rate	100 kg/hectare	
	Pollutant concentration ^d	100 mg/kg	
	Annual pollutant loading rate	5.0 kg/hectare per 365-day period	
	Toxic chemical release reporting; Community Right-to-Know; effective date	01/01/87	EPA 2001q 40CFR372.65
STATE			
Regulations and Guidelines:			
a. Air			
Hawaii	HAP		BNA 2001

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Illinois	Toxic air contaminant		BN A 2001
Kansas	HAP		BN A 2001
Kentucky	HAP		BN A 2001
Maryland	Toxic air pollutant Selenium sulfide		BN A 2001
Minnesota	HAP threshold—de minimis level Selenium compounds Selenium sulfide	0.1 ton/year 0.1 ton/year	BN A 2001
Nebraska	HAP—effective date	12/15/98	BN A 2001
New Hampshire	Regulated toxic air pollutant		BN A 2001
New Mexico	Toxic air pollutant OEL Emissions	0.2 mg/m ³ 0.0133 mg/m ³	BN A 2001
New York	HAP—selenium compounds		BN A 2001
Rhode Island	HAP		BN A 2001
South Carolina	Toxic air emissions—maximum allowable concentration Selenium compounds	1 µg/m ³	BN A 2001
Vermont	Hazardous ambient air standards Annual average Action level	4.80 µg/m ³ 0.40 pounds/8-hours	BN A 2001
Washington	HAP—threshold levels Selenium and compounds Selenium hexafluoride Selenium sulfides	0.5 tons/year 0.5 tons/year 0.5 tons/year	BN A 2001
b. Water			
Alabama	Aquatic life criteria Freshwater Acute Chronic Marine Acute Chronic MCL Primary drinking water standard	20 µg/L 5.0 µg/L 300 µg/L 71 µg/L 0.05 mg/L 0.01 mg/L	BN A 2001
Alaska	Groundwater cleanup level MCL	0.05 mg/L 0.05 mg/L	BN A 2001
Arizona	Aquifer water quality standards Drinking water guideline MCL Water quality standards Conversion factor ^e for saltwater—acute criteria Conversion factor ^e for saltwater—chronic criteria	0.05 mg/L 45 µg/L 0.05 mg/L 0.998 0.998	BN A 2001 HSDB 2001 BN A 2001 EPA 2001r 40CFR131.38

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Colorado	Groundwater protection—MCL	0.01 mg/L	BN A 2001
	MCL	0.05 mg/L	BN A 2001
	Primary drinking water standard	0.01 mg/L	BN A 2001
Connecticut	MCL	0.05 mg/L	BN A 2001
Delaware	Groundwater protection—MCL	0.01 mg/L	BN A 2001
	Primary drinking water standard	0.01 mg/L	BN A 2001
Florida	MCL	0.05 mg/L	BN A 2001
Georgia	MCL	0.05 mg/L	BN A 2001
Hawaii	MCL	0.05 mg/L	BN A 2001
	Water quality criteria applicable to all waters		BN A 2001
	Freshwater		
	Acute	20 µg/L	
	Chronic	5.0 µg/L	
	Saltwater		
	Acute	300 µg/L	
	Chronic	71 µg/L	
Illinois	Concentration shall not be exceeded in water	1.0 mg/L	BN A 2001
	Groundwater quality standard	0.01 mg/L	BN A 2001
	MCL	0.05 mg/L	BN A 2001
Indiana	MCLG	0.05 mg/L	BN A 2001
	MCL	0.05 mg/L	
Iowa	MCL	0.05 mg/L	BN A 2001
Kansas	Surface water quality standard		BN A 2001
	Aquatic life		
	Acute	20 µg/L	
	Chronic	5.0 µg/L	
	Agriculture		
	Livestock	50 µg/L	
	Irrigation	20 µg/L	
	Public health food		
	Procurement	6,800 µg/L	
	Domestic water supply	50 µg/L	
Kentucky	Domestic water supply use—maximum allowable instream concentration	0.05 mg/L	BN A 2001
	MCL	0.05 mg/L	BN A 2001
	Maximum groundwater contaminant level	0.01 mg/L	BN A 2001
Kentucky	Primary drinking water standard	0.01 mg/L	BN A 2001
	Warm water aquatic habitat criteria		BN A 2001
	Acute		
	Chronic	20 µg/L 5.0 µg/L	

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Louisiana	Groundwater protection—MCL	0.01 mg/L	BNA 2001
Maine	Drinking water guideline	10 µg/L	HSDB 2001
Maryland	Criteria for toxic substances in surface waters		BNA 2001
	Freshwater		
	Acute	20 µg/L	
	Chronic	5.0 µg/L	
	Saltwater		
	Acute	300 µg/L	
	Chronic	71 µg/L	
	Drinking water	50 µg/L	
	MCL	0.05 mg/L	BNA 2001
	Primary drinking water standard	0.01 mg/L	BNA 2001
Massachusetts	Environmental toxicity values		BNA 2001
	Freshwater		
	Acute	20 µg/L	
	Chronic	5.0 µg/L	
	Marine		
	Acute	300 µg/L	
	Chronic	71 µg/L	
	Groundwater protection—MCL	0.01 mg/L	BNA 2001
	MCL	0.05 mg/L	BNA 2001
Michigan	MCL	0.05 mg/L	BNA 2001
	Effective date	07/30/92	
Minnesota	Drinking water guideline	30 µg/L	HSDB 2001
Mississippi	Groundwater standard	50 ppb	BNA 2001
	Water quality criteria—concentration shall not exceed	0.01 mg/L	BNA 2001
Montana	MCL	0.05 mg/L	BNA 2001
North Carolina	Fresh surface water quality standard for Class C waters	5.0 µg/L	BNA 2001
	Groundwater quality standard	0.05 mg/L	BNA 2001
Nebraska	Aquatic life		BNA 2001
	Acute	20 µg/L	
	Chronic	5.0 µg/L	
	Water supply	0.05 mg/L	BNA 2001
	MCL	0.05 mg/L	BNA 2001
New Hampshire	Groundwater quality standard	0.05 mg/L	
	MCLG	0.05 mg/L	BNA 2001
	MCL	0.05 mg/L	

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
New Hampshire	Water quality criteria Protection of aquatic life Fresh acute chronic Marine acute chronic Protection of human health Water and fish ingestion	 5.0 µg/L 290µg/L 71 µg/L 170 µg/L 11,000 µg/L	 BNA 2001
New Mexico	MCL	0.05 mg/L	BNA 2001
Nevada	Domestic water supply Dissolved selenium	 0.05 mg/L	 BNA 2001
New York	MCL	0.05 mg/L	BNA 2001
North Dakota	MCL	0.05 mg/L	BNA 2001
Ohio	Groundwater concentration limit	0.01 mg/L	BNA 2001
Oklahoma	Public and private water supplies Fish and wildlife propagation Acute Chronic	 20 µg/L 5.0 µg/L	 BNA 2001
Rhode Island	Groundwater quality standard Preventive action limit	 0.05 mg/L 0.025 mg/L	 BNA 2001
South Carolina	MCL	0.05 mg/L	BNA 2001
South Dakota	Groundwater maximum allowable concentration Aquatic life value Acute Chronic	 20 µg/L 5.0 µg/L	 BNA 2001
Tennessee	Groundwater criteria concentration MCL	 0.05 mg/L 0.05 mg/L	 BNA 2001
Texas	MCL	0.05 mg/L	BNA 2001
Utah	MCL Water quality Domestic Agriculture	 0.01 mg/L 0.05 mg/L	 BNA 2001
Vermont	Groundwater quality standards Enforcement standard Preventive action level MCLG MCL	 50 µg/L 25 µg/L 0.05 mg/L 0.05 mg/L	 BNA 2001

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Vermont	Water quality criteria for protection of aquatic organisms Maximum allowable concentration Acute Average allowable concentration Chronic	20 µg/L 5.0 µg/L	BNA 2001
Virginia	Groundwater protection levels Protection level Monitoring level MCL Surface water criteria Freshwater Acute Chronic Saltwater Acute Chronic Human health Public water supplies All other surface waters	10 µg/L 5.0 µg/L 0.01 mg/L 170 µg/L 11,000 µg/L	BNA 2001 BNA 2001 BNA 2001 BNA 2001
Washington	MCL	0.05 mg/L	BNA 2001
Wisconsin	Groundwater quality standards Enforcement standard Preventive action limit MCL	50 µg/L 10 µg/L 0.05 mg/L	BNA 2001 BNA 2001 BNA 2001
Wyoming	Water quality Aquatic life Acute Chronic Human health	20 µg/L 5.0 µg/L 10 µg/L	BNA 2001
c. Food			
New York	Bottled water sampling requirements—MCL	0.01 mg/L	BNA 2001
d. Other			
Alabama	Identification and listing of hazardous waste		BNA 2001
Arizona	Soil remediation levels Residential Non-residential	380 mg/kg 8,500 mg/kg	BNA 2001
California	Hazardous waste injection restrictions—waste specific prohibitions Selenium and/or compounds	100 mg/L	EPA 2001s 40CFR148.12 (b)(2)

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
California	Known to cause cancer or reproductive toxicity—initial appearance of chemical on list Selenium sulfide	10/01/89	BNA 2001
	Total threshold limit concentration	10,000 mg/kg	BNA 2001
Delaware	Regulated toxic substance—sufficient quantity Selenium hexafluoride	900 pounds/hour	BNA 2001
Florida	Toxic substance in the workplace Hydrogen selenium Selenium Selenium hexafluoride Selenium oxychloride Selenium sulfide		BNA 2001
Hawaii	Restricted use pesticides Selenium compounds	All concentrations	BNA 2001
Kentucky	Threshold planning quantity Hydrogen selenide Selenious acid Selenium oxychloride	10 pounds 1,000/10,000 pounds 500 pounds	BNA 2001
Massachusetts	Oil and hazardous material Selenious acid Selenium and compounds Selenium dioxide Selenium disulfide Selenium oxide Selenium oxychloride Selenium sulfide Selenourea		BNA 2001
Minnesota	RfD Health risk limit	0.005 mg/kg/day 30 µg/L	BNA 2001
New Hampshire	Restricted use pesticide	All concentrations	BNA 2001
New Jersey	Extraordinary hazardous substance—threshold quantity Selenium hexafluoride	700 pounds	BNA 2001

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Selenium

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Oregon	Toxic substance—de minimis concentration	1.0 percent	BNA 2001
Vermont	Restricted use pesticide Selenium and compounds	All concentrations	BNA 2001

^aGroup 3: not classifiable as to its carcinogenicity to humans^bGroup D: not classifiable as to its carcinogenicity to humans^cGroup B2: probable human carcinogen^dMonthly average concentrations^eConversion factors are based on a hardness of 100 mg/L as calcium carbonate

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HAP = hazardous air pollutant; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; RDA = recommended daily allowance; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1^* —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL—from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose₍₅₀₎ (TD₅₀)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Selenium
CAS Number: 7782-49-2 (elemental)
Date: June 5, 2003
Profile Status: Post Public Comments, Draft 3
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Graph Key: 101
Species: Human

Minimal Risk Level: 0.005 ☒ mg/kg/day ☐ ppm

Reference: Yang G, Zhou R. 1994. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electrolytes Health Dis 8:159-165.

Experimental design: This study was an examination of a group of five individuals who were recovering from selenosis, and who had been drawn from a larger population studied by the same authors (Yang et al. 1989a, 1989b). Yang et al. (1989a, 1989b) examined a population in an area of China where selenosis occurred. Data were collected on selenium levels in the diet, blood, nails, hair, urine, and milk of residents, and the incidence of clinical symptoms of selenosis (morphological changes in fingernails) was compared with dietary intake of selenium and selenium levels in blood. Selenium levels in blood corresponded to the dietary intake of selenium, and symptoms of selenosis occurred at or above a selenium intake level of 910 µg/day (0.016 mg/kg/day) (Yang et al 1989a). In 1992, Yang and Zhou (1994) reexamined five individuals from the high selenium site who had been suffering from symptoms of selenosis (loss of fingernails and hair), but were recovering (nails were regrowing). Since their earlier report, the living conditions of the population had improved; they had been cautioned against consuming high selenium foods and parts of their locally produced corn had been replaced with rice or cereals. Yang and Zhou (1994) found that the mean concentration of selenium in the blood of these selenosis patients had fallen from 1,346 µg/L (measured in 1986) to 968 µg/L (measured in 1992). Using a regression equation derived from the data in their earlier report (Yang et al. 1989b) and average body weights of 55 kg, Yang and Zhou (1994) calculated that the mean dietary intake of selenium associated with selenosis in these individuals was 1,270 µg/day (LOAEL of 0.023 mg/kg/day), while a mean intake of 819 µg selenium/day (NOAEL of 0.015 mg/kg/day) was associated with recovery.

Effects noted in study and corresponding doses: A NOAEL of 0.015 mg/kg/day for nail disease based on recovery from symptoms of selenosis, and a LOAEL of 0.023 mg/kg/day based on nail damage were calculated from selenium concentrations in blood using average body weights of 55 kg and the regression equation: $Y_{\text{blood-Se}} (\text{mg/L}) = 8230 \times 10^{-4} X_{\text{se-intake}} (\mu\text{g}) + 0.176$ derived in Yang et al. (1989b).

Dose and end point used for MRL derivation: 0.015 mg/kg/day; nail disease (selenosis)

☒ NOAEL ☐ LOAEL

Uncertainty Factors used in MRL derivation:

- ☐ 10 for use of a LOAEL
- ☐ 10 for extrapolation from animals to humans
- ☒ 3 for human variability

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A factor of 3 was considered appropriate because the individuals in this report were sensitive individuals drawn from the larger population in the Yang et al. (1989a, 1989b) studies and because of the supporting studies described below.

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

NA

Other additional studies or pertinent information which lend support to this MRL:

Yang et al. (1989a, 1989b) examined a population of 349 individuals in an area of China where selenosis occurred. They collected data on selenium levels in the diet, blood, nails, hair, urine, and milk of residents at three sites with low, medium, and high selenium, and compared the incidence of clinical symptoms of selenosis (morphological changes in finger nails) with dietary intake of selenium and selenium levels in blood. They found that selenium levels in blood corresponded to the dietary intake of selenium, and that symptoms of selenosis were found at or above a selenium intake level of 910 $\mu\text{g/day}$ (0.016 mg/kg/day) (Yang et al 1989a). The population included adult men and women, teenagers, children, and infants. High selenium levels were found in individuals of all ages, but symptoms of selenosis were generally confined to adults (97% of cases) and were never observed in children younger than 12 years of age (Yang et al. 1989b). The manifestation of symptoms of selenosis was not solely dependent on selenium intake, but was subject to individual variability, as individuals who exhibited selenosis did not necessarily have the highest blood selenium levels.

Longnecker et al. (1991) examined two groups of adults (142 individuals) in areas of Wyoming and South Dakota with elevated selenium intake. The average daily intake of selenium in this population was 239 $\mu\text{g/day}$ (0.003 mg/kg/day) and some individuals consumed as much as 724 $\mu\text{g/day}$ (0.01 mg/kg/day). The highest blood concentration of selenium noted in this population was 0.67 mg/kg, a concentration lower than the 1.05 mg/L concentration associated with effects in China. No symptoms of selenosis or any other significant health effects associated with selenium exposure were reported for individuals in this study. This study suggests that the estimates of dietary intake of selenium produced by the regression equation in Yang et al. (1989b) may be conservative. Longnecker et al. (1991) reported doses of 68–724 $\mu\text{g/day}$ associated with blood concentrations of 0.18–0.67 mg/kg. If the doses from the Longnecker et al. (1991) study are placed in the regression equation from Yang et al. (1989b), blood concentrations of 0.14 and 0.88 mg/L are calculated. If it is assumed that a liter of blood weighs approximately 1 kg, then this regression equation overpredicts blood levels of selenium at the higher doses in the population from North Dakota. This provides support for additional exposure (e.g., inhalation exposure) in the Chinese population that was not accounted for in the regression equation.

Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones (St. Germain and Galton 1997). Two human studies were located that describe significant decreases in triiodothyronine levels in response to elevated selenium; however, the hormone levels observed in these studies were subclinical within the normal human range and the biological significance of the effect is not clear. In the first study, Brätter and Negretti De Brätter (1996) examined a Venezuelan population with high selenium intake. Serum, erythrocyte, toenail, and breast milk selenium concentrations were determined for 65 women living in three seleniferous regions of Venezuela. Selenium dietary intakes were determined from the selenium concentration of breast milk by regression (Brätter et al. 1991), and free thyroxine (T_4), free triiodothyronine (T_3), and human thyroid stimulating hormone (TSH) levels were measured. Selenium intake ranged from 170 to 980 $\mu\text{g/day}$. There was a significant inverse correlation between free T_3 and selenium levels in serum (Spearman R

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test), but free T₃, free T₄, and TSH levels were found to be within normal ranges. No symptoms of selenosis were found in the women included in this study.

In the second human study, serum hormone, semen, immunological, and hematological status was evaluated in a 120-day double blind study of healthy men (20–45 years old) who consumed a controlled diet of foods naturally low or high in selenium (Hawkes and Turek 2001; Hawkes et al. 2001). Eleven subjects were fed a diet that provided 47 µg Se/day (0.0006 mg/kg/day) for the first 21 days of the study. For the following 99 days, six of the subjects were fed a diet providing 13 µg Se/day (0.0002 mg/kg/day), and five of the remaining subjects were fed a diet providing 297 µg/day (0.004 mg/kg/day). Comprehensive evaluations were performed at weeks 3 (baseline), 17 (ending value), and several interim time points on end points that included selenium levels (in blood plasma, erythrocytes, seminal plasma, and sperm); thyroid hormone levels (serum T₃ and TSH); reproductive hormone levels (serum testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone); semen quality (sperm concentration, semen volume, sperm total number, fraction motile sperm, percent progressive sperm, mean forward velocity, and various sperm morphology parameters); immunological indices (complete blood counts, lymphocyte phenotypes, serum immunoglobulins (IgA, IgG, IgM); complement fractions; peripheral blood mononuclear cell (PBMNC) *in vitro* proliferative responses to mitogenic stimulation with phytohemagglutinin (PHA), concanavalin A (ConA), and pokeweed; natural-killer cell (NKC) activity; delayed-type hypersensitivity (DHS) skin responses to recall antigens (tuberculin purified-protein derivative, mumps, tetanus toxoid, candida, trichophyton, streptokinase streptase, and coccidioidin); antibody responses to diphtheria-tetanus and influenza vaccines); and hematological indices (complete blood counts, white blood cells, lymphocytes, granulocytes, platelets, erythrocytes, hematocrit, and hemoglobin concentration). For measurements repeated more than twice, the baseline value was subtracted from the value at each time point to calculate within-subject changes, and two-way repeated measures analysis of variance was used to test for significant effects of dietary selenium and time. When the selenium main effect or the selenium x time interaction was significant, the Student-Newman-Keuls comparison test was used to identify significant differences between the low-selenium and high-selenium groups at individual time points. For measurements obtained only twice (during baseline and at end of study), within-subject changes were compared between groups with a two-tailed t-test. Measurements obtained only at the end of the study were compared between groups with a two-tailed t-test without any correction. A probability of ≤0.05 was considered significant in all tests.

Selenium levels in blood plasma began to change within 3 days of starting the low- and high-selenium diets and progressively continued throughout the study (Hawkes and Turek 2001). By week 17, mean plasma selenium concentrations had increased by 109% in the high-selenium group and decreased by 38.5% in the low-selenium group. Group mean serum T₃ concentrations (averages of within-subject changes from baseline) were significantly different in the low-selenium subjects and high-selenium subjects at all time points, but the magnitudes of the changes are insufficient to be considered biologically significant in either group. In the low-selenium group, serum T₃ levels increased an average of 14 and 8% from baseline during weeks 8 and 17, respectively. In the high-selenium group, serum T₃ levels decreased an average of 23 and 11% from baseline during weeks 8 and 17, respectively. Analysis of variance (ANOVA) indicated a significant effect of dietary selenium on serum T₃ concentrations and that the magnitude of the effect was modified by the duration of exposure (i.e., the group changes in T₃ levels decreased over time). Although the decreases in serum T₃ in the high selenium group and increases in serum T₃ in the low selenium group lessened in magnitude during the study, all group mean values appear to have remained within the normal range (only week 17 values were actually reported). The respective baseline and week 17 serum T₃ values (mean±SD) were 1.82±0.36 and 1.57±0.07 nmol/L in the high-selenium group and 1.57±0.25 and 1.64±0.16 nmol/L in the low-selenium group, compared to a normal human range of 1.1–2.7 nM/L for total T₃, indicating that the changes were subclinical and not biologically significant. Serum TSH concentrations increased significantly by 32% over its baseline concentration in the high-selenium group but did not change significantly in the low-selenium group.

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Baseline and ending TSH values in the high-selenium group were 2.25 ± 0.81 and 2.96 ± 1.05 mU/L, respectively, both of which are in the normal range of 0.3–4.0 mU/L (Stockigt 2000). There were no significant changes in the serum levels, nor any significant differences between groups in free or total testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, or progesterone.

The pattern of changes in seminal plasma selenium levels was similar to that observed for blood selenium, although selenium levels in sperm did not change significantly in either group (Hawkes and Turek 2001). Mean sperm motility (average of within-subject changes from baseline in fraction of motile sperm) was significantly different in the low-selenium subjects and high-selenium subjects at week 13, but not at weeks 8 or 17. The fraction of motile sperm increased an average of 10% in the low-selenium group at week 13, and was essentially the same as baseline at week 17. Sperm motility decreased an average of 32% in the high-selenium group at week 13, and ended 17% lower than the baseline value at week 17. The ANOVA indicated a significant effect of dietary selenium on sperm motility and that the effect of selenium was modified by duration of exposure (the groups diverged over time). Baseline and ending motile sperm fractions in the high-selenium group were 0.588 ± 0.161 and 0.488 ± 0.193 , respectively; >50% motility is considered normal (FDA 1993). The decrease in sperm motility in the high-selenium group cannot be clearly attributed to exposure because the effect was not related to duration of treatment, and is unlikely to be adverse because the effect is at the low end of the normal range and not accompanied by any significant effects of high- or low-selenium treatment on sperm progression, concentration, total number, or morphology. Additionally, there were no effects of selenium on serum levels of the reproductive hormones, and changes in the thyroid hormones, which could also affect sperm function, were not outside normal ranges.

The immunological assessment showed that the high-selenium diet was not immunotoxic and had some mild and transient immune-enhancing properties (Hawkes et al. 2001). There is an indication that selenium supplementation increased the secondary immune response to diphtheria vaccine when rechallenged at the end of the study. The mean within-subject ratio of diphtheria antibody titers 14 days after reinoculation (day 116) to titers 14 days after the initial challenge at baseline (day 19) was significantly greater in the high-selenium group than in the low-selenium group (2.7 ± 1.8 -fold vs. 0.9 ± 0.6 -fold, $p=0.03$). Lymphocyte counts were significantly increased in the high-selenium group on day 45, but not at the end of the study, and there were no clear effects of selenium on numbers of activated or cytotoxic T-cells. The proliferative response of peripheral lymphocytes to stimulation with pokeweed mitogen (a B-cell mitogen) was significantly higher in the high-selenium group than in the low-selenium group on days 45 and 72, although not at the end of the study. There was no selenium-induced lymphocyte proliferation in response to the T-cell mitogens (phytohemagglutinin or concanavalin A) or changes in any of the other immunological end points. The hematological assessment (Hawkes et al. 2001) found minor mean within-subject changes from baseline in white blood cell counts that were significantly different in the low- and high-selenium groups at the last two time points (days 70 and 99); WBCs were decreased by 5% in the high-selenium group and increased by 10% in the low-selenium group at the end of the study. The changes in WBC counts were due mainly to changes in granulocytes. Lymphocyte counts were significantly increased in the high-selenium group on day 45, but not at the end of the study.

Chemical Manager: John Risher, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

- (1) **Route of Exposure** One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
- (2) **Exposure Period** Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) **Health Effect** The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) **Key to Figure** Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).
- (5) **Species** The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) **Exposure Frequency/Duration** The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) **System** This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

- (8) **NOAEL** A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) **LOAEL** A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) **Reference** The complete reference citation is given in Chapter 9 of the profile.
- (11) **CEL** A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) **Footnotes** Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) **Exposure Period** The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) **Health Effect** These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) **Levels of Exposure** concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) **NOAEL** In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

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- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

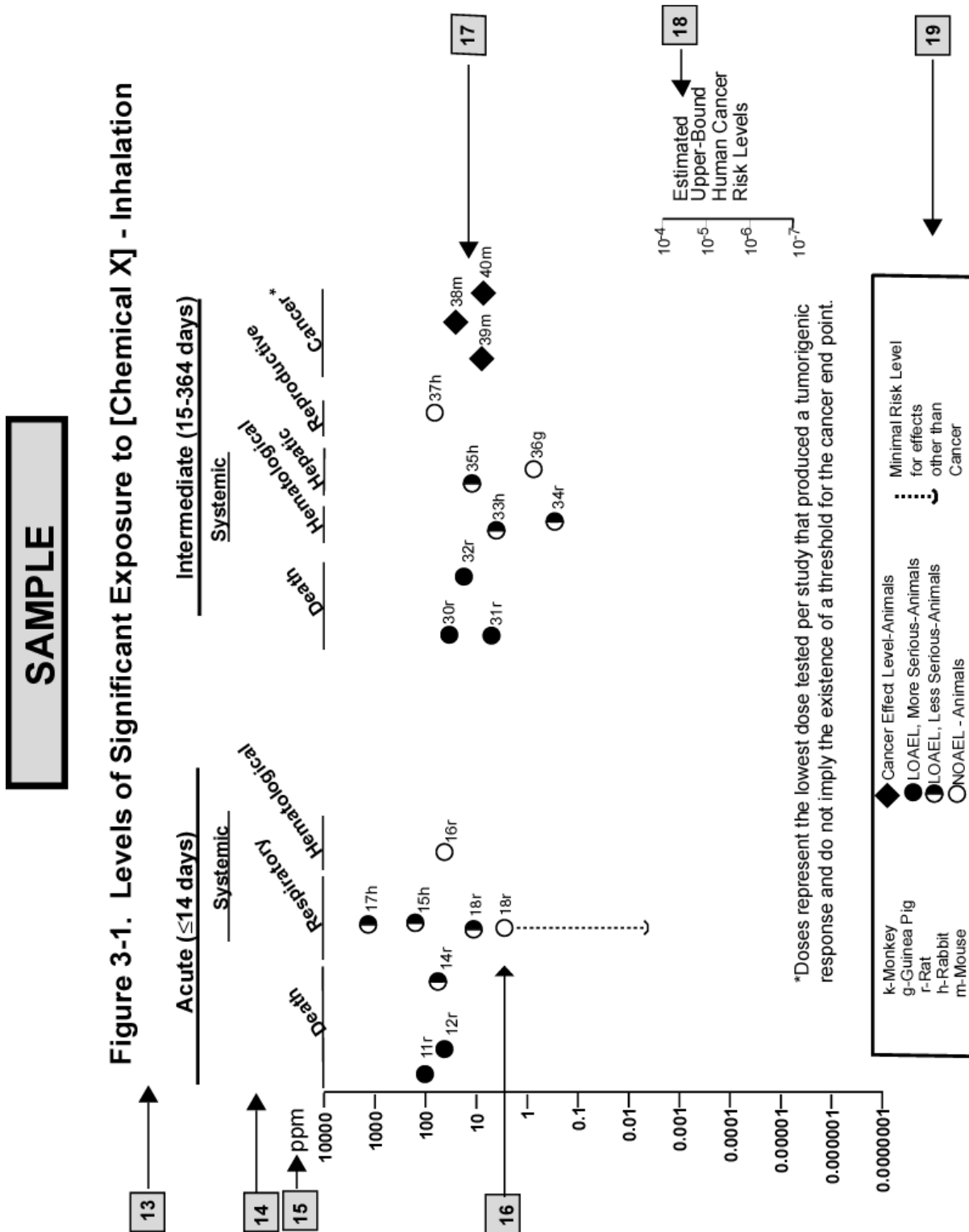
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SAMPLE

TABLE 3-1. Levels of Significant Exposure to [Chemical x] - Inhalation

	Key to figure ^a	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
						Less serious (ppm)	Serious (ppm)	
1	↑							
2	↑							
INTERMEDIATE EXPOSURE								
3	↑	Systemic	↓	↓	↓	↓	↓	↓
4	↑	18 Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE								
Cancer								
38		Rat	18 mo 5 d/wk 7 hr/d			20 (CEL, multiple organs)		Wong et al. 1982
39		Rat	89-104 wk 5 d/wk 6 hr/d			10 (CEL, lung tumors, nasal tumors)		NTP 1982
40		Mouse	79-103 wk 5 d/wk 6 hr/d			10 (CEL, lung tumors, hemangiosarcomas)		NTP 1982
12	↑							

^a The number corresponds to entries in Figure 3-1.^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANOVA	analysis of variance
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

APPENDIX C

DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	<i>Federal Register</i>
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
GPX	glutathione peroxidase
GSH	glutathione
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K _d	adsorption ratio
kg	kilogram
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT ₅₀	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie

APPENDIX C

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA

APPENDIX C

PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	pictogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
RDA	Recommended Daily Allowance
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RR	relative risk
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
T ₃	triiodothyronine
T ₄	thyroxine
TD ₅₀	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSH	thyroid stimulating hormone
TWA	time-weighted average
UF	uncertainty factor
UL	Tolerable Upper Intake Level
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound

APPENDIX C

WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q ₁ *	cancer slope factor
−	negative
+	positive
(+)	weakly positive result
(−)	weakly negative result

TOXICOLOGICAL PROFILE FOR CADMIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2012

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for Cadmium, Draft for Public Comment was released in September 2008. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the toxic substances each profile describes. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The profiles focus on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. A health effects summary describes the adequacy of information to determine a substance's health effects. ATSDR identifies data needs that are significant to protection of public health.

Each profile:

- (A) Examines, summarizes, and interprets available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) Determines whether adequate information on the health effects of each substance is available or being developed to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identifies toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are federal, state, and local health professionals; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other federal scientists also have reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Christopher J. Portier, Ph.D.
Assistant Administrator

Agency for Toxic Substances and Disease Registry

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 **How Can (Chemical X) Affect Children?**

Section 1.7 **How Can Families Reduce the Risk of Exposure to (Chemical X)?**

Section 3.7 **Children's Susceptibility**

Section 6.6 **Exposures of Children**

Other Sections of Interest:

Section 3.8 **Biomarkers of Exposure and Effect**

Section 3.11 **Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) **Fax:** (770) 488-4178

E-mail: cdcinfo@cdc.gov

Internet: <http://www.atsdr.cdc.gov>

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Environmental Toxicology Branch (proposed) reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for cadmium. The panel consisted of the following members:

1. Maryka H. Bhattacharyya, Ph.D., Senior Biochemist, Biosciences Division (BIO), Argonne National Laboratory, Lemont, Illinois 60439,
2. Masayuki Ikeda, Ph.D., M.D., Professor, Kyoto Industrial Health Association, Kyoto, Japan 604-8472, and
3. Zahir A Shaikh, Ph.D., Professor of Pharmacology and Toxicology, Director of the Center for Molecular Toxicology, University of Rhode Island, Kingston, Rhode Island 02881.

These experts collectively have knowledge of cadmium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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This public health statement tells you about cadmium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Cadmium has been found in at least 1,014 of the 1,669 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which cadmium is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to cadmium or cadmium compounds, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

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1.1 WHAT IS CADMIUM?

Description	<p>Metal found in the earth's crust, associated with zinc, lead, and copper ores.</p> <p>Pure cadmium is a soft, silver-white metal. Cadmium chloride and cadmium sulfate are soluble in water.</p>
Uses <ul style="list-style-type: none">• Manufacturing• Consumer products	<p>Most cadmium used in the United States is extracted as a byproduct during the production of other metals such as zinc, lead, or copper. Cadmium is also recovered from used batteries.</p> <p>Cadmium is used for the following:</p> <ul style="list-style-type: none">• batteries (83%)• pigments (8%)• coatings and platings (7%)• stabilizers for plastics (1.2%)• nonferrous alloys, photovoltaic devices, and other uses (0.8%)

For more information on the properties and uses of cadmium, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO CADMIUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	<p>Cadmium is emitted to soil, water, and air by non-ferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal.</p> <p>Cadmium can accumulate in aquatic organisms and agricultural crops.</p>
Fate <ul style="list-style-type: none">• Air• Soil• Water	<p>Cadmium (as oxide, chloride, and sulfate) will exist in air as particles or vapors (from high temperature processes). It can be transported long distances in the atmosphere, where it will deposit (wet or dry) onto soils and water surfaces.</p> <p>Cadmium and its compounds may travel through soil, but its mobility depends on several factors such as pH and amount of organic matter, which will vary depending on the local environment. Generally, cadmium binds strongly to organic matter where it will be immobile in soil and be taken up by plant life, eventually, entering the food supply.</p> <p>Cadmium exists as the hydrated ion or as ionic complexes with other inorganic or organic substances. Soluble forms migrate in water. Insoluble forms of cadmium are immobile and will deposit and absorb to sediments.</p>

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1.3 HOW MIGHT I BE EXPOSED TO CADMIUM?

Food and smoking—primary sources of exposure	<p>In the United States, for nonsmokers the primary source of cadmium exposure is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes and grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium, approximately 0.05–0.12 mg cadmium/kg.</p> <p>Tobacco leaves accumulate high levels of cadmium from the soil.</p> <p>The national geometric mean blood cadmium level for adults is 0.38 µg/L. A geometric mean blood cadmium level of 1.58 µg/L for New York City smokers has been reported. The amount of cadmium absorbed from smoking one pack of cigarettes per day is about 1–3 µg/day. Direct measurement of cadmium levels in body tissues confirms that smoking roughly doubles cadmium body burden in comparison to not smoking.</p>
Air	<p>Except for people living near cadmium-emitting industries, inhalation of cadmium is not expected to be a major concern.</p>
Water	<p>Elevated cadmium levels in water sources in the vicinity of cadmium-emitting industries (historical and current) have been reported. Aquatic organisms will accumulate cadmium, possibly entering the food supply. People who fish in local waters as a means of food should be cautious and abide by any advisories.</p>
Occupational exposure	<p>Highest risk of exposure from processes involving heating cadmium-containing materials such as smelting and electroplating. Risk will vary depending on the workplace.</p> <p>Major route of exposure is through inhalation of dust and fumes or incidental ingestion from contaminated hands, food, or cigarettes.</p> <p>Exposure can be controlled through personal protective equipment, good industrial hygiene practices, and control and reduction of cadmium emissions.</p>

In Chapter 6, you can find more information on how you might be exposed to cadmium.

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1.4 HOW CAN CADMIUM ENTER AND LEAVE MY BODY?

Enter your body <ul style="list-style-type: none"> • Inhalation • Ingestion • Dermal contact 	<p>About 5–50% of the cadmium you breathe will enter your body through your lungs.</p> <p>A small amount of the cadmium in food and water (about 1–10%) will enter your body through the digestive tract. If you do not have enough iron or other nutrients in your diet, you are likely to take up more cadmium from your food than usual.</p> <p>Virtually no cadmium enters your body through your skin.</p>
Leave your body	<p>Most of the cadmium that enters your body goes to your kidney and liver and can remain there for many years. A small portion of the cadmium that enters your body leaves slowly in urine and feces.</p> <p>Your body can change most cadmium to a form that is not harmful, but too much cadmium can overload the ability of your liver and kidney to change the cadmium to a harmless form.</p>

More information on how cadmium enters and leaves the body is found in Chapter 3.

1.5 HOW CAN CADMIUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Workers <ul style="list-style-type: none"> • Inhalation 	<p>Breathing air with very high levels of cadmium can severely damage the lungs and may cause death.</p> <p>Breathing air with lower levels of cadmium over long periods of time (for years) results in a build-up of cadmium in the kidney, and if sufficiently high, may result in kidney disease.</p>
Laboratory animals <ul style="list-style-type: none"> • Inhalation 	<p>Damage to the lungs and nasal cavity has been observed in animals exposed to cadmium.</p>

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Humans • Oral	<p>Eating food or drinking water with very high cadmium levels severely irritates the stomach, leading to vomiting and diarrhea, and sometimes death.</p> <p>Eating lower levels of cadmium over a long period of time can lead to a build-up of cadmium in the kidneys. If the build-up of cadmium is high enough, it will damage the kidneys.</p> <p>Exposure to lower levels of cadmium for a long time can also cause bones to become fragile and break easily.</p>
Laboratory animals • Oral	<p>Kidney and bone effects have also been observed in laboratory animals ingesting cadmium.</p> <p>Anemia, liver disease, and nerve or brain damage have been observed in animals eating or drinking cadmium. We have no good information on people to indicate what cadmium levels people would need to eat or drink to result in these diseases, or if they would occur at all.</p>
Cancer	<p>Lung cancer has been found in some studies of workers exposed to cadmium in the air and studies of rats that breathed in cadmium.</p> <p>The U.S. Department of Health and Human Services (DHHS) has determined that cadmium and cadmium compounds are known human carcinogens. The International Agency for Research on Cancer (IARC) has determined that cadmium is carcinogenic to humans. The EPA has determined that cadmium is a probable human carcinogen.</p>

More information on how cadmium can affect your health is found in Chapters 2 and 3.

1.6 HOW CAN CADMIUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

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Effects in children	<p>The health effects seen in children from exposure to toxic levels of cadmium are expected to be similar to the effects seen in adults (kidney and lung damage).</p> <p>Harmful effects on child development or behavior have not generally been seen in populations exposed to cadmium, but more research is needed.</p> <p>A few studies in animals indicate that younger animals absorb more cadmium than adults. Animal studies also indicate that the young are more susceptible than adults to a loss of bone and decreased bone strength from exposure to cadmium.</p> <p>Cadmium is found in breast milk and a small amount will enter the infant's body through breastfeeding. The amount of cadmium that can pass to the infant depends on how much exposure the mother may have had.</p>
Birth defects	<p>We do not know whether cadmium can cause birth defects in people.</p> <p>Studies in animals exposed to high enough levels of cadmium during pregnancy have resulted in harmful effects in the young. The nervous system appears to be the most sensitive target. Young animals exposed to cadmium before birth have shown effects on behavior and learning. There is also some information from animal studies that high enough exposures to cadmium before birth can reduce body weights and affect the skeleton in the developing young.</p>

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CADMIUM?

Do not smoke tobacco products	<p>Cadmium accumulates in tobacco leaves. The national geometric mean blood cadmium level for adults is 0.376 µg/L. Mean blood cadmium levels for heavy smokers have been reported as high as 1.58 µg/L.</p>
Good occupational hygiene	<p>Occupational exposure can be controlled through personal protective equipment, good industrial hygiene practices, and control and reduction of cadmium emissions.</p> <p>Children can be exposed to cadmium through parents who work in cadmium-emitting industries. Therefore, good hygiene practices such as bathing and changing clothes before returning home may help reduce the cadmium transported from the job to the home.</p>
Avoid cadmium contaminated areas and food	<p>Check and obey local fishing advisories before consuming fish or shellfish from local waterways.</p> <p>Avoid hazardous waste sites.</p>

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Proper disposal of cadmium-containing products	Dispose of nickel-cadmium batteries properly. Many states have laws in effect that ban the disposal of batteries as municipal waste. Recycle old batteries whenever possible. Contact your local waste and recycling authority on how to properly dispose of paints and coatings.
Handle properly	Do not allow children to play with batteries. If mishandled, batteries could rupture. Children may also swallow small nickel-cadmium batteries.

If your doctor finds that you have been exposed to significant amounts of cadmium, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CADMIUM?

Detecting exposure	Cadmium can be measured in blood, urine, hair, or nails. Urinary cadmium has been shown to accurately reflect the amount of cadmium in the body.
Measuring exposure	The amount of cadmium in your blood shows your recent exposure to cadmium. The amount of cadmium in your urine shows both your recent and your past exposure. Cadmium levels in hair or nails are not as useful as an indication of when or how much cadmium you may have taken in, partly because cadmium from outside of your body may attach to the hair or nails. Tests are also available to measure the amount of cadmium inside your liver and kidneys.

More information on how cadmium can be measured in exposed humans is presented in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National

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Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for cadmium include the following:

Drinking water	<p>The EPA has determined that exposure to cadmium in drinking water at a concentration of 0.04 mg/L for up to 10 days is not expected to cause any adverse effects in a child.</p> <p>The EPA has determined that lifetime exposure to 0.005 mg/L cadmium in drinking water is not expected to cause any adverse effects.</p>
Consumer products	The FDA has determined that cadmium levels in bottled water should not exceed 0.005 mg/L.
Workplace air	OSHA set a legal limit of 5 µg/m ³ cadmium in air averaged over an 8-hour work day.

More information on governmental rules regarding cadmium can be found in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

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ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: <http://www.ntis.gov/>

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CADMIUM IN THE UNITED STATES

Cadmium occurs in the earth's crust at a concentration of 0.1–0.5 ppm and is commonly associated with zinc, lead, and copper ores. It is also a natural constituent of ocean water with average levels between <5 and 110 ng/L, with higher levels reported near coastal areas and in marine phosphates and phosphorites. The cadmium concentration of natural surface water and groundwater is usually <1 µg/L. Surface soil concentrations will depend on several factors such as its mobility, natural geochemistry, and magnitude of contamination from sources such as fertilizers and atmospheric deposition. Natural emissions of cadmium to the environment can result from volcanic eruptions, forest fires, generation of sea salt aerosols, or other natural phenomena.

In the environment, cadmium exists in only one oxidation state (+2) and does not undergo oxidation-reduction reactions. In surface water and groundwater, cadmium can exist as the hydrated ion or as ionic complexes with other inorganic or organic substances. Soluble forms of cadmium can migrate in water. Insoluble forms of cadmium will settle and adsorb to sediments. Cadmium's fate in soil depends on several factors such as pH of the soil and the availability of organic matter. Generally, cadmium will bind strongly to organic matter and this will, for the most part, immobilize it. However, cadmium's behavior in soil will vary depending on the environmental conditions. It is not likely that cadmium will undergo significant transformation in the atmosphere. It will exist in particulate form and sometimes vapor form (emitted from high temperature processes) where it will undergo atmospheric transport and eventually deposit onto soils and surface waters.

Non-ferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of cadmium in the environment. Except for those who live near cadmium-emitting industries, inhalation of cadmium in the ambient air may occur, but is not a major source of exposure. Water sources near cadmium-emitting industries, both with historic and current operations, have shown a marked elevation of cadmium in water sediments and aquatic organisms. Concentrations of cadmium in these polluted waters have ranged from <1.0 to 77 µg/L. For the U.S. population, cadmium exposure through the drinking water supply is of minor concern. Cadmium from polluted soil and water can accumulate in plants and organisms, thus entering the food supply.

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In the United States, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake. The estimated daily intakes of cadmium in nonsmoking adult males and females living in the United States are 0.35 and 0.30 $\mu\text{g Cd/kg/day}$, respectively. Females generally absorb greater amounts of cadmium in the gastrointestinal tract. In general, leafy vegetables such as lettuce and spinach and staples such as potatoes and grains contain relatively high values of cadmium. Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium. People who regularly consume shellfish and organ meats (liver and kidney) have increased cadmium exposure.

Mean values of cadmium in the blood and urine of the U.S. population were reported in the National Health and Nutrition Examination Survey (NHANES) 1999–2008. Blood cadmium tends to reflect recent exposures and urinary cadmium reflects cumulative cadmium exposure and body burden (particularly, kidney cadmium levels). The 20 years or older age group had geometric mean levels of blood and urine cadmium that were slightly higher than the younger age groups (0.376 $\mu\text{g/L}$ in blood and 0.232 $\mu\text{g/L}$ in urine). Females (0.331 $\mu\text{g/L}$ in blood and 0.191 $\mu\text{g/L}$ in urine) had slightly higher blood and urine cadmium levels than males (0.299 $\mu\text{g/L}$ in blood and 0.179 $\mu\text{g/L}$ in urine).

Smoking greatly increases exposure to cadmium, as tobacco leaves naturally accumulate high amounts of cadmium. It has been estimated that tobacco smokers are exposed to 1.7 μg cadmium per cigarette, and about 10% is inhaled when smoked. A geometric mean blood cadmium level for a heavy smoker has been reported as high as 1.58 $\mu\text{g/L}$, compared to the estimated national mean of 0.38 $\mu\text{g/L}$ for all adults. Nonsmokers may also be exposed to cadmium in cigarettes via second-hand smoke.

2.2 SUMMARY OF HEALTH EFFECTS

Since the early 1950s, when the hazards of occupational cadmium exposure were recognized, a large amount of information has been generated concerning the toxic effects of cadmium exposure in humans and laboratory animals. Toxicological properties of cadmium are similar for the several different salts and oxides of cadmium that have been investigated, although differences in absorption and distribution lead to different effect levels. For inhalation exposure, particle size and solubility in biological fluids (in contrast to solubility in water) appear to be the more important determinants of the toxicokinetics. For oral exposure, most experimental studies have used soluble cadmium, which exists as the Cd^{+2} ion regardless of the initial salt. Absorption appears to be similar for cadmium ion and cadmium complexed with proteins in food, except for a few specific types of foods such as Bluff oysters and seal meat. Also, poorly soluble cadmium pigments may be absorbed to a lesser extent than soluble cadmium ion. For the

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general population, dietary exposure to cadmium is the most likely route of exposure. There is an extensive database on the toxicity of cadmium in environmentally exposed populations and in cadmium workers; however, most of these studies were focused on the presumed sensitive targets. These sensitive targets of cadmium toxicity are the kidney and bone following oral exposure and kidney and lung following inhalation exposure. Studies in animals support the identification of these sensitive targets and provide some suggestive evidence that the developing organisms may also be a sensitive target. There is also evidence to suggest that cadmium is a human carcinogen. Other effects that have been observed in humans and/or animals include reproductive toxicity, hepatic effects, hematological effects, and immunological effects.

The earliest indication of kidney damage in humans is an increased excretion of low molecular weight proteins, particularly β 2-microglobulin, human complex forming glycoprotein (pHC) (also referred to as α 1-microglobulin), and retinol binding protein; increased urinary levels of intracellular enzymes such as N-acetyl- β -glucosaminidase (NAG); and increased excretion of calcium and metallothionein. Numerous studies of cadmium workers and populations living in areas with low, moderate, or high cadmium pollution have found significant associations between urinary cadmium levels and biomarker levels or significant increases in the prevalence of abnormal biomarker levels. At higher exposure levels, decreases in glomerular filtration rate, increased risk of renal replacement therapy (dialysis or kidney transplantation), and significant increases in the risk of deaths from renal disease have been observed. The sensitivity of the kidney to cadmium is related to its distribution in the body and *de novo* synthesis of metallothionein in the kidney. In the blood, cadmium is bound to metallothionein and is readily filtered at the glomerulus and reabsorbed in the proximal tubule. Within the tubular cells, the metallothionein is degraded in lysosomes and free cadmium is released; the synthesis of endogenous metallothionein by the tubular cells is then stimulated. However, when the total cadmium content in the renal cortex reaches between 50 and 300 $\mu\text{g/g}$ wet weight, the amount of cadmium not bound to metallothionein becomes sufficiently high to cause tubular damage. Free cadmium ions may inactivate metal-dependent enzymes, activate calmodulin, and/or damage cell membranes through activation of oxygen species. Because the toxicity of cadmium is dependent on its concentration in the kidney, adverse effects in humans are typically not observed after shorter durations.

Acute inhalation exposure to cadmium at concentrations above about 5 mg/m^3 may cause destruction of lung epithelial cells, resulting in pulmonary edema, tracheobronchitis, and pneumonitis in both humans and animals. A single, high-level cadmium exposure can result in long-term impairment of lung function. At the cellular level, catalase, superoxide dismutase, non-protein sulfhydryl, glucose-6-phosphate

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dehydrogenase, and glutathione peroxidase are decreased in response to cadmium lung insults. The respiratory response to cadmium is similar to the response seen with other agents that produce oxidative damage. There typically is an alveolar pneumocyte type 2 cell hyperplasia in response to type 1 cell damage and necrosis. Longer-term inhalation exposure at lower levels also leads to decreased lung function and emphysema in cadmium workers. Some tolerance to cadmium-induced lung irritation develops in exposed humans and animals, and respiratory function may recover after cessation of cadmium exposure. Another effect of long-term inhalation cadmium exposure is damage to the olfactory function and nasal epithelium. Lung damage has also been seen in a few studies of oral cadmium exposure in rats, but the lung effects are likely to be related to liver or kidney damage and subsequent changes in cellular metabolism.

Prolonged inhalation or ingestion exposure of humans to cadmium at levels causing renal dysfunction can lead to painful and debilitating bone disease in individuals with risk factors such as poor nutrition; the occurrence of these bone effects in elderly Japanese women exposed to high levels of cadmium in rice and water was referred to as Itai-Itai disease. Decreases in bone mineral density, increases in the risk of fractures, and increases in the risk of osteoporosis have also been observed in populations living in cadmium-polluted areas. An association between bone effects and cadmium exposure has also been observed in populations exposed to higher levels of cadmium, but not living in cadmium polluted areas. Similar effects have also been observed in young rats orally exposed to cadmium. Animal data strongly suggest that cadmium exposure results in increases in bone turnover and decreases in mineralization during the period of rapid bone growth. Although animal studies suggest that these effects are due to direct damage to the bone, it is likely that renal damage resulting in the loss of calcium and phosphate and alteration in renal metabolism of vitamin D would compound these effects.

There are few human data on developmental effects from exposure to cadmium. Some studies indicate that maternal cadmium exposure may cause decreased birth weight in humans, but most of these studies are of limited use because of weaknesses in the study design and lack of control for confounding factors. A number of other studies did not find a significant relationship between maternal cadmium levels and newborn body weight. In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes. Decreased fetal weight, skeletal malformations, and delayed ossification are produced by relatively high maternal doses (1–20 mg/kg/day) due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver. Neurodevelopmental effects have been observed at lower doses. Impaired performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg/m³ or ≥0.04 mg/kg/day.

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The results of occupational exposure studies examining the possible association between cadmium exposure and an increased risk of lung cancer are inconsistent, with some studies finding significant increases in lung cancer deaths and other studies not finding increases. Interpretation of the results of many of the studies is complicated by inadequate controls for confounding factors such as co-exposure with other metal carcinogens and smoking, small number of lung cancer deaths, and the lack of significant relationships between cadmium exposure and duration. For prostate cancer, initial studies in European workers indicated an elevation in prostate cancer, but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant. Strong evidence from animal studies exists that cadmium inhalation can cause lung cancer, but only in rats. Most oral studies in laboratory animals have not found significant increases in cancer incidence. The Department of Health and Human Services concluded that there were sufficient human and animal data to conclude that cadmium is a known human carcinogen; likewise, IARC classified cadmium as carcinogenic to humans (Group 1). The EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1), based on its assessment of limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for cadmium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990d), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

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bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The database on the toxicity of cadmium in humans and animals following inhalation or oral exposure is extensive. Target organs are similar among species and, in general, toxicokinetic properties after oral and inhalation exposures are similar. Most of the human data involve chronic inhalation exposure of workers or chronic dietary exposure of the general population or populations living in cadmium-polluted areas. Several approaches for characterizing cadmium exposure have been used in these studies. Occupational exposure studies have used current air concentrations or have estimated cumulative exposure based on historical and current monitoring data. Some epidemiology studies have estimated cumulative intake based on the levels of cadmium in rice, in populations where rice has been the dominant source of oral exposure to cadmium. However, most studies (particularly oral studies) have used urinary cadmium levels as a biomarker of exposure. As discussed in greater detail in Section 3.8.1, urinary cadmium levels correlate with cadmium body burden and cadmium concentration in kidney (a critical target organ for chronic exposure). The relationship between renal and urinary cadmium appears to be nearly linear at chronic intakes and kidney burdens that do not produce nephrotoxicity (i.e., elimination half-time is independent of dose). However, at high kidney cadmium burdens, associated with renal damage ($>50 \mu\text{g Cd/g cortex}$), the elimination half-time increases with increasing severity of renal damage. Linearity in the dose-urinary excretion relationship also does not appear to apply following an acute high exposure to cadmium. The Nordberg-Kjellström model (described in detail in Section 3.4.5.3) is a multicompartiment pharmacokinetic model that can be used to estimate cadmium intakes (inhalation and oral exposure) associated with a given urinary cadmium level and/or kidney cadmium burden. The model has been extensively evaluated for predicting dose-kidney-urinary cadmium relationships within the linear range of the dose-urinary cadmium relationship.

Inhalation MRLs***Acute-Duration Inhalation MRL***

- An MRL of $3 \times 10^{-5} \text{ mg Cd/m}^3$ ($0.03 \mu\text{g Cd/m}^3$) has been derived for acute-duration inhalation exposure (<14 days) to cadmium.

The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial

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symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986b) estimated that an 8-hour exposure to 1–5 mg/m³ would be immediately dangerous.

Animal studies support the findings in humans that acute exposure to cadmium results in lung damage. Single exposures to approximately 1–10 mg Cd/m³ as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m³ 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). Lower concentrations of 0.4–0.5 mg Cd/m³ as cadmium oxide for 2–3 hours (Buckley and Bassett 1987b; Grose et al. 1987) or 0.17 mg Cd/m³ as cadmium chloride 6 hours/day for 10 days (Klimisch 1993) resulted in mild hypercellularity and increases in lung weight. Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m³ as cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m³ (NTP 1995). At similar concentrations (0.19 or 0.88 mg Cd/m³ as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1–2 hours (Graham et al. 1978; Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m³ as cadmium carbonate for 2 hours (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m³ as cadmium oxide for 2 hours (Rusch et al. 1986).

The NTP (1995) study was selected as the basis of an acute duration inhalation MRL. In this study, groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m³ (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m³) 6.2 hours/day, 5 days/week for 2 weeks. The mean median aerodynamic diameter (MMAD) of the cadmium oxide particles was 1.5 µm with a geometric standard deviation of 1.6–1.8. The animals were observed twice daily and weighed on days 1, 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates). All rats in the 8.8 mg Cd/m³ group died by day 6; no other deaths occurred. A slight decrease in terminal body weights was observed at 2.6 mg Cd/m³; however, the body weights were within 10% of control weights. Significant increases in relative

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and absolute lung weights were observed at 0.26 (males only), 0.88, and 2.6 mg Cd/m³. Histological alterations were limited to the respiratory tract and consisted of alveolar histiocytic infiltrate and focal inflammation and minimal fibrosis in alveolar septa at ≥ 0.088 mg Cd/m³, necrosis of the epithelium lining alveolar ducts at ≥ 0.26 mg Cd/m³, tracheobronchial lymph node inflammation at ≥ 0.88 mg Cd/m³, degeneration of the nasal olfactory epithelium at 0.88 mg Cd/m³, and inflammation and metaplasia of the nasal respiratory epithelium at 2.6 mg Cd/m³.

The lowest-observed-adverse-effect level (LOAEL) of 0.088 mg Cd/m³ was selected as the point of departure for derivation of the MRL; benchmark dose analysis was considered; however, the data were not suitable for benchmark dose analysis because the data do not provide sufficient information about the shape of the dose-response relationship below the 100% response level. The LOAEL_{HEC} was calculated using the equations below.

$$\text{LOAEL}_{\text{HEC}} = \text{LOAEL}_{\text{ADJ}} \times \text{RDDR}$$

The duration-adjusted LOAEL (LOAEL_{ADJ}) was calculated as follows:

$$\begin{aligned}\text{LOAEL}_{\text{ADJ}} &= 0.088 \text{ mg Cd/m}^3 \times 6.2 \text{ hours/24 hours} \times 5 \text{ days/7 days} \\ \text{LOAEL}_{\text{ADJ}} &= 0.016 \text{ mg Cd/m}^3\end{aligned}$$

The regional deposited dose ratio (RDDR) for the pulmonary region of 0.617 was calculated with EPA's RDDR calculator (EPA 1994a) using the final body weight of 0.194 kg for the male rats exposed to 0.088 mg Cd/m³, the reported MMAD of 1.5 μm and the midpoint of the reported range of geometric standard deviations (1.7).

$$\begin{aligned}\text{LOAEL}_{\text{HEC}} &= 0.016 \text{ mg Cd/m}^3 \times 0.617 \\ \text{LOAEL}_{\text{HEC}} &= 0.01 \text{ mg Cd/m}^3\end{aligned}$$

The LOAEL_{HEC} was divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability) resulting in an acute-duration inhalation MRL of 3×10^{-5} mg Cd/m³ (0.03 μg Cd/m³).

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Intermediate-Duration Inhalation MRL

There are no studies examining the intermediate-duration toxicity of inhaled cadmium in humans; however, numerous animal studies have identified several targets of cadmium toxicity. Increases in the number of bronchioalveolar macrophages, alveolar histiocytic infiltration, degeneration or metaplasia in the larynx, and proliferations have been observed in rats and mice exposed to 0.022 mg Cd/m³ as cadmium oxide or cadmium chloride (Glaser et al. 1986; NTP 1995; Prigge 1978a). At higher concentrations (>0.88 mg Cd/m³), marked inflammation and fibrosis was observed in lungs of rats (Kutzman et al. 1986; NTP 1995). In general, these studies did not identify no-observed-adverse-effect levels (NOAELs) for lung effects. The NTP (1995) study also found significant increases in the incidence of inflammation of the nasal respiratory epithelium in rats exposed to 0.22 mg Cd/m³ and degeneration of the nasal olfactory epithelium in mice exposed to 0.088 mg Cd/m³. The NTP (1995) study did not find any histological alterations in non-respiratory tract tissues, alterations in urinalysis parameters, or changes in blood pressure (rats only) in rats or mice. Prigge (1978a, 1978b) reported increases in hemoglobin and hematocrit levels in rats continuously exposed to ≥ 0.052 mg Cd/m³; however, this effect was not observed in the NTP (1995) studies. Reproductive effects (increased duration of estrous cycle and decreased spermatid counts) have also been observed at higher concentrations (0.88–1 mg Cd/m³) (Baranski and Sitarek 1987; NTP 1995).

The studies by Baranski (1984, 1985) provide suggestive evidence that the developing organism is also a sensitive target of cadmium toxicity. Significant alterations in performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg Cd/m³ as cadmium oxide 5 hours/day, 5 days/week for 5 months prior to mating, during a 3-week mating period, and during gestation days 1–20. No other studies examined neurodevelopmental end points following inhalation exposure. However, the identification of neurodevelopmental effects as a sensitive target of cadmium toxicity is supported by several intermediate-duration animal studies finding neurodevelopmental effects including alterations in motor activity and delays in the development of sensory motor coordination reflexes (Ali et al. 1986; Baranski 1985; Desi et al. 1998; Nagymajtenyi et al. 1997). Other developmental effects observed in the inhalation studies included decreases in fetal body weight in the fetuses of rats exposed to 1.7 or 0.581 mg Cd/m³ (NTP 1995; Prigge 1978b) and mice exposed to 0.4 mg Cd/m³ (NTP 1995).

Based on the available animal data, the LOAEL of 0.022 mg Cd/m³ for lung and larynx effects in mice (NTP 1995) and the LOAEL of 0.02 mg Cd/m³ for neurodevelopmental effects (Baranski 1984, 1985) were evaluated as possible points of departure for the intermediate-duration inhalation MRL for cadmium.

The LOAEL of 0.022 mg Cd/m³ identified in the NTP (1995) mouse study was considered as the point of departure for the MRL because the NTP study provided more study details and information on particle size distribution. Because an MRL based on this LOAEL (LOAEL_{HEC} of 1 µg Cd/m³) would be lower than the chronic-duration inhalation MRL based on human data, an intermediate-duration inhalation MRL was not derived.

Chronic-Duration Inhalation MRL

- An MRL of 0.01 µg Cd/m³ has been derived for chronic-duration inhalation exposure (≥1 year) to cadmium.

Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations included an increase in residual volume in workers exposed to air concentrations of cadmium fumes ranging from 0.008 (in 1990) to 1.53 mg/m³ (in 1975) (mean urinary cadmium level in the workers was 4.3 µg/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034–0.156 mg/m³ (Davison et al. 1988); and decreased force vital capacity in workers exposed to >0.2 mg/m³ (Smith et al. 1976). Additionally, Chan et al. (1988) found significant improvements in several parameters of lung function of workers following reduction or cessation of cadmium exposure.

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as NAG, amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate (GFR). The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight proteins (particularly, β₂-microglobulin, retinol binding protein, and pHc) in cadmium workers, as compared to levels found in a reference group of workers or the general population (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al.

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1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Although increases in the excretion of low molecular weight proteins are not diagnostic of renal damage (Bernard et al. 1997; Järup et al. 1998b), tubular proteinuria is considered an adverse effect because it is an early change in a sequence of events which ultimately may result in compromised renal function (Bernard et al. 1997). Most investigators consider a 10% cadmium-associated increase in the prevalence of abnormal levels of renal biomarkers (urinary β 2-microglobulin, retinol binding protein, pHc) to be indicative of cadmium-induced renal disease in the population. However, there is less consensus on the low molecular protein level regarded as elevated or abnormal (cut-off point).

Several biomarkers of tubular damage have been used in occupational exposure studies; these include β 2-microglobulin, retinol binding protein, NAG, and pHc. Of these biomarkers, which differ in their sensitivities to detect tubular damage, β 2-microglobulin is the most widely used in occupational exposure studies. In healthy humans, urinary β 2-microglobulin levels are $<300 \mu\text{g}/24 \text{ hours}$ (approximately $300 \mu\text{g}/\text{g creatinine}$). Four studies have estimated the prevalence of abnormal urinary β 2-microglobulin levels among cadmium workers using cut-off levels of $187\text{--}380 \mu\text{g}/\text{g creatinine}$ (Chen et al. 2006a; Elinder et al. 1985a; Jakubowski et al. 1987; Järup and Elinder 1994). The prevalence of abnormal urinary β 2-microglobulin levels was 10% among workers with urinary cadmium levels of $1.5 (\geq 60 \text{ years of age})$ or $5 (<60 \text{ years of age}) \mu\text{g}/\text{g creatinine}$ (β 2-microglobulin cut-off level of $220 \mu\text{g}/\text{g creatinine}$) (Järup and Elinder 1994), 25% among workers with urinary cadmium levels of $2\text{--}5 \mu\text{g}/\text{g creatinine}$ (cut-off level of $300 \mu\text{g}/\text{g creatinine}$) (Elinder et al. 1985a), 40% among workers with urinary cadmium levels of $5\text{--}10 \mu\text{g}/\text{g creatinine}$ (cut-off level of $187 \mu\text{g}/\text{g creatinine}$) (Chen et al. 2006a), and 10% among workers with urinary cadmium levels of $10\text{--}15 \mu\text{g}/\text{g creatinine}$ (cut-off level of $380 \mu\text{g}/\text{g creatinine}$) (Jakubowski et al. 1987). A 10% prevalence of abnormal β 2-microglobulin levels (cut-off level of $300 \mu\text{g}/\text{g creatinine}$) was also observed in workers with a cumulative blood cadmium level of $300 \mu\text{g}\text{-years}/\text{L}$ (30 years of $10 \mu\text{g}/\text{L}$) (Jakubowski et al. 1992) or blood cadmium level of $5.6 \mu\text{g}/\text{L}$ (cumulative exposure of $691 \mu\text{g}\text{-years}/\text{m}^3$) (Järup et al. 1988).

Most of the studies reporting respiratory effects expressed cadmium exposure as air concentrations; however, these air concentrations may not be indicative of cadmium exposure over time. For example, in the Cortona et al. (1992) study, cadmium levels of $0.030 \text{ mg}/\text{m}^3$ were measured in 1990 in one foundry; in 1976, the cadmium levels in this foundry were $1.53 \text{ mg}/\text{m}^3$. Cortona et al. (1992) also reported cadmium body burden data; the mean urinary cadmium level in the workers was $4.3 \mu\text{g}/\text{L}$ (roughly equivalent to $4 \mu\text{g}/\text{g creatinine}$). Renal effects have been observed at similar cadmium burdens. Most studies have

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reported renal effects in workers with urinary cadmium levels of ≥ 5 $\mu\text{g/g}$ creatinine; Järup and Elinder (1994) found an increased prevalence of low molecular weight proteinuria in workers ≥ 60 years of age with mean urinary cadmium of 1.5 $\mu\text{g/g}$ creatinine. The air concentration that would result in this urinary cadmium level would be considered a LOAEL. However, cadmium in the workplace air was not the only source of cadmium. The workers were also exposed to other sources of cadmium (e.g., cadmium in the diet); both sources contributed to the renal cadmium burden. Thus, in order to calculate a chronic-duration inhalation MRL from the LOAEL identified in the Järup and Elinder (1994) study, the workers' other sources of cadmium need to be taken into consideration; this information was not reported in the study.

An alternative approach would be to use environmental exposure studies to establish a point of departure for the urinary cadmium-renal response relationship and pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) to predict cadmium air concentrations. As described in greater detail in the chronic oral MRL section, a meta-analysis of available environmental exposure studies was conducted to estimate an internal dose (urinary cadmium expressed as $\mu\text{g/g}$ creatinine) corresponding to a 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). For the inhalation MRL, the meta-analysis also included dose-response data from three occupational exposure studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). Analysis of the environmental exposure studies resulted in an estimation of a urinary cadmium level that would result in a 10% increase in the prevalence of $\beta 2$ -microglobulin proteinuria (1.34 $\mu\text{g/g}$ creatinine); the 95% lower confidence limit on this value was 0.5 $\mu\text{g/g}$ creatinine. The UCD_{10} values from the occupational exposure studies were 7.50 $\mu\text{g/g}$ creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 $\mu\text{g/g}$ creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). Because the dose-response analysis using the European environmental exposure studies provided the lowest UCD_{10} , it was selected for derivation of the chronic-duration inhalation MRL; the 95% lower confidence limit on this value (UCDL_{10}) of 0.5 $\mu\text{g/g}$ creatinine was used as the point of departure for the MRL.

Deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition, retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow, S; moderate, M; or fast, F). Cadmium compounds are classified as follows: oxides and hydroxides, S; sulfides, halides and nitrates, M; all other, including chloride salts, F.

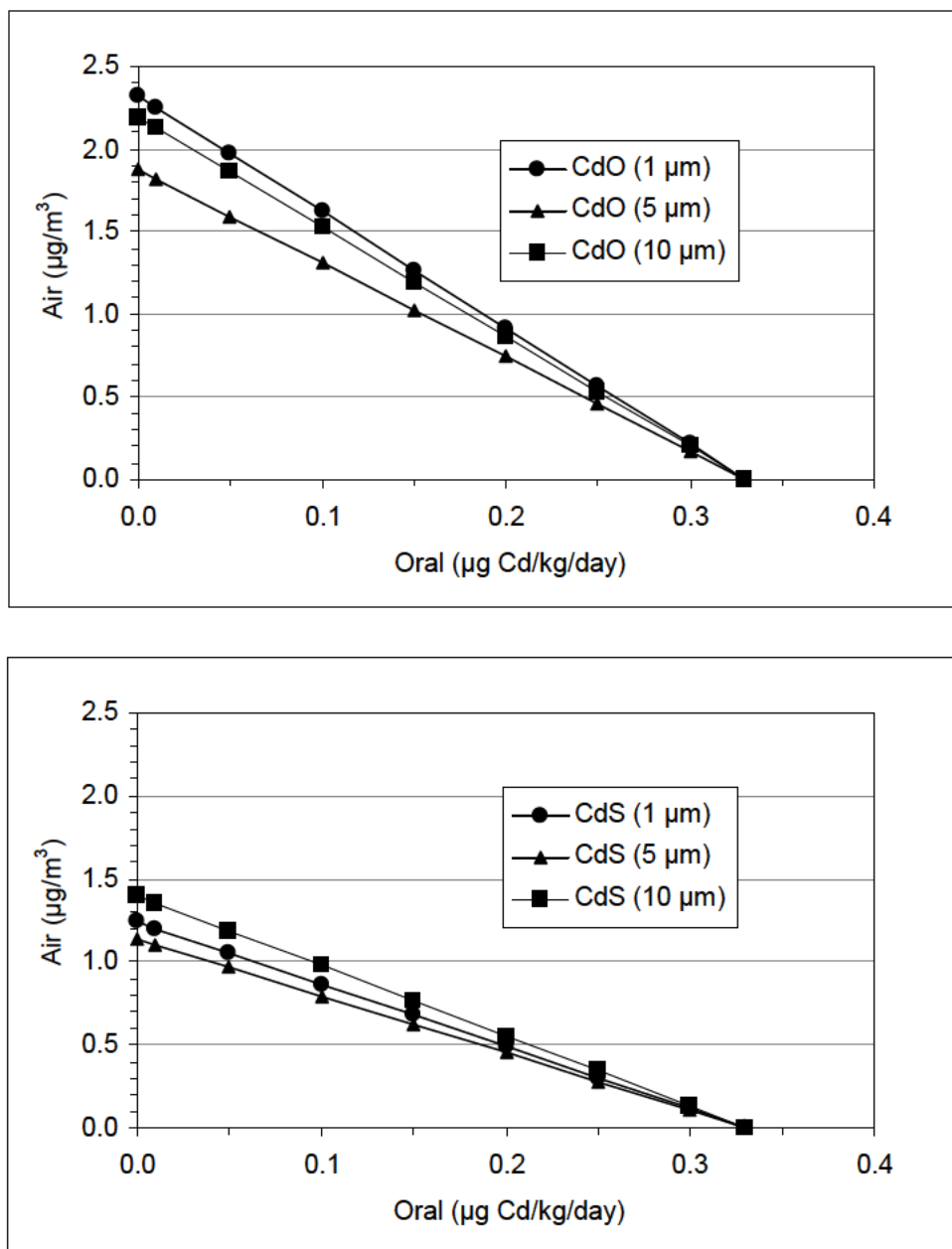
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Inhalation exposures ($\mu\text{g}/\text{m}^3$) to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μg (AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucociliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Nordberg-Kjellström pharmacokinetic model (Kjellström and Nordberg 1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure.

As illustrated in [Figure 2-1](#), an airborne cadmium concentration of 1.8–2.4 $\mu\text{g}/\text{m}^3$ as cadmium oxide or 1.2–1.4 $\mu\text{g}/\text{m}^3$ as cadmium sulfide would result in a urinary cadmium level of 0.5 $\mu\text{g}/\text{g}$ creatinine, assuming that there was no dietary source of cadmium. This assumption is not accurate because the diet is a significant contributor to the cadmium body burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in non smoking males and females in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively (0.32 $\mu\text{g}/\text{kg}/\text{day}$ for males and females combined) (estimated from data in Choudhury et al. 2001). Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (activity median aerodynamic diameter [AMAD]=1 μm) and oral intakes that yield the same urinary cadmium level ([Figure 2-1](#)), exposure to an airborne cadmium concentration of 0.1 $\mu\text{g}/\text{m}^3$ and a dietary intake of 0.3 $\mu\text{g}/\text{kg}/\text{day}$ would result in a urinary cadmium level of 0.5 $\mu\text{g}/\text{g}$ creatinine. Dividing this cadmium air concentration (0.1 μg Cd/ m^3) by an uncertainty factor of 3 for human variability and a modifying factor of 3 results in chronic-duration inhalation MRL of 0.01 μg Cd/ m^3 . The uncertainty factor of 3 for human variability was used to account for the possible increased sensitivity of diabetics (Åkesson et al. 2005; Buchet et al. 1990) and the modifying factor of 3 was used to account for the lack of adequate human data, which could be used to compare the relative sensitivities of the respiratory tract and kidneys. Although based on exposure to cadmium sulfide, the MRL would be protective of exposure to cadmium oxide; the pharmacokinetic models predict that exposure to 0.1 $\mu\text{g}/\text{m}^3$ as cadmium oxide (AMAD=1 μm) in combination with a dietary intake of 0.3 $\mu\text{g}/\text{kg}/\text{day}$ would result in a urinary cadmium level of 0.4 $\mu\text{g}/\text{g}$ creatinine.

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Figure 2-1. Combined Chronic Oral Cadmium Intakes ($\mu\text{g}/\text{kg}/\text{day}$) and Inhalation Cadmium Exposures ($\mu\text{g}/\text{m}^3$) that Achieve a Urinary Cadmium Excretion of $0.5 \mu\text{g}/\text{g}$ Creatinine at Age 55 Years Predicted by the Cadmium Pharmacokinetic Model and the International Commission on Radiological Protection (ICRP) Human Respiratory Tract Model*



*The upper panel shows simulations of inhalation exposures to cadmium oxide (AMAD=1, 5, or 10 μm); the lower panel shows simulations of inhalation cadmium sulfide aerosols.

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Oral MRLs***Acute-Duration Oral MRL***

There are no reliable studies on the acute toxicity of cadmium in humans; animal studies have identified several targets of toxicity. High exposures (>10 mg Cd/kg/day) to cadmium chloride administered via gavage or drinking water resulted in increases in hematological (increased hemoglobin, hematocrit, and erythrocytes, anemia), liver (focal necrosis and degeneration), kidney (focal necrosis of tubular epithelium), intestine (necrosis, hemorrhage, ulcers), stomach (gastritis, necrosis), neurological (decreased motor activity), and testicular (atrophy and necrosis, loss of spermatogenic elements) effects and decreases in body weight in rats and mice (Andersen et al. 1988; Basinger et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989; Dixon et al. 1976; Kotsonis and Klaassen 1977; Machemer and Lorke 1981; Sakata et al. 1988; Shimizu and Morita 1990). The NOAELs for these effects ranged from 1.12 to 65.6 mg Cd/kg/day.

Developmental effects have been observed at lower cadmium doses. Delayed ossification of the sternum and ribs was observed in the offspring of rats administered 2 mg Cd/kg/day via gavage on gestation days 7–16; at 40 mg Cd/kg/day, fused lower limbs, decreased number of live fetuses, and increased resorptions were observed (Baranski 1985). A significant increase in malformations was observed in the offspring of rats administered 18.39 mg Cd/kg/day on gestation days 6–15 (Machemer and Lorke 1981); no developmental effects were observed in the offspring of rats administered 12.5 mg Cd/kg/day via drinking water on gestation days 6–15 (Machemer and Lorke 1981).

Although the Baranski (1985) study identified the lowest LOAEL (2 mg Cd/kg/day) following acute-duration exposure, this study was not considered suitable for derivation of an MRL. The investigators noted that “a retarded process of ossification of the sternum and ribs was observed after exposure to cadmium at any of the doses used.” However, the data were not shown and the statistical significance of the finding was not reported. Additionally, an intermediate-duration study conducted earlier by this investigator (Baranski et al. 1983) did not find delays in ossification in the offspring of rats administered up to 4 mg Cd/kg/day for 5 weeks prior to mating, during the 3-week mating period, and throughout gestation.

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Because of the amount of uncertainty associated with the most sensitive end point, an acute-duration oral MRL was not derived.

Intermediate-Duration Oral MRL

- An MRL of 0.5 µg Cd/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to cadmium.

There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure. Numerous animal studies have examined the systemic, immunological, neurological, reproductive, and developmental toxicity of cadmium. The most sensitive systemic effect following intermediate-duration oral exposure to cadmium appears to be damage to growing bone. Exposure to 0.2 mg Cd/kg/day as cadmium chloride in drinking water for 3–12 months resulted in decreases in bone mineral density, impaired mechanical strength of the lumbar spine, tibia, and femur bones, increased bone turnover, and increased incidence of deformed or fractured lumbar spine bone in young female rats (3 weeks of age at study initiation) (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c, 2010); similar findings were observed in young male rats exposed to 0.5 mg Cd/kg/day for up to 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Decreases in bone strength were also observed in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi et al. 1989); however, no skeletal effects were observed in adult or elderly female rats exposed to doses >20 mg Cd/kg/day for 4 weeks (Ogoshi et al. 1989). Decreases in bone calcium were observed in mice undergoing repeated pregnancy/lactation periods (Bhattacharyya et al. 1988b) or ovariectomized mice (Bhattacharyya et al. 1988c); these changes were not observed in groups not under physiological stress.

Renal effects have been observed at higher doses than the skeletal effects. Vesiculation of the proximal tubules was observed in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks (Gatta et al. 1989). At approximately 3–8 mg Cd/kg/day, proteinuria, tubular necrosis, and decreased renal clearance were observed in rats (Cha 1987; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a). Liver necrosis and anemia (Cha 1987; Groten et al. 1990; Kawamura et al. 1978) were observed at similar cadmium doses.

Immunological effects have been observed in studies of monkeys, rats, and mice. The observed effects include increases in cell-mediated immune response in monkeys exposed to 5 mg Cd/kg/day as cadmium chloride in the diet for 10 weeks (Chopra et al. 1984), decreased humoral immune response in mice

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exposed to 2.8 mg Cd/kg/day as cadmium chloride in drinking water for 3 weeks (Blakley 1985), and greater susceptibility to lymphocytic leukemia virus in mice exposed to 1.9 mg Cd/kg/day as cadmium chloride in drinking water for 280 days (Blakley 1986).

Neurological effects observed in rats include decreases in motor activity at 3.1 or 9 mg Cd/kg/day (Kotsonis and Klaassen 1978; Nation et al. 1990) and increased passive avoidance at 5 mg Cd/kg/day (Nation et al. 1984). Reproductive effects (necrosis and atrophy of seminiferous tubules, decreased sperm count and motility) were observed in rats exposed to 8–12 mg Cd/kg/day (Cha 1987; Saxena et al. 1989).

A number of developmental effects have been observed in the offspring of rats exposed to cadmium during gestation and lactation. Decreases in glomerular filtration rates and increases in urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium were observed in 60-day-old offspring of rats administered via gavage 0.5 mg Cd/kg/day on gestation days 1–21 (Jacquillet et al. 2007). Neurodevelopmental alterations have also been observed at the low maternal doses. Delays in the development of sensory motor coordination reflexes and increased motor activity were observed at 0.706 mg Cd/kg/day (gestation days 1–21) (Ali et al. 1986), decreased motor activity at 0.04 mg Cd/kg/day (5–8 weeks of pre-gestation exposure, gestation days 1–21) (Baranski et al. 1983), decreased ambulation and rearing activity and altered ECG at 14 mg Cd/kg/day (gestation days 5–15, lactation days 2–28, postnatal days 1–56) (Desi et al. 1998) or 7 mg Cd/kg/day (F_2 and F_3 generations) (Nagymajtenyi et al. 1997) have been observed. Decreases in pup body weight were observed at ≥ 5 mg Cd/kg/day (Baranski 1987; Gupta et al. 1993; Kostial et al. 1993; Pond and Walker 1975) and decreases in fetal body weight or birth weight were observed at ≥ 2.4 mg Cd/kg/day (Petering et al. 1979; Sorell and Graziano 1990; Webster 1978; Sutou et al. 1980). Another commonly reported developmental effect was alterations in hematocrit levels or anemia in the offspring of animals exposed to ≥ 1.5 mg Cd/kg/day (Baranski 1987; Kelman et al. 1978; Webster 1978). Increases in the occurrence of malformations or anomalies is limited to a study by Sutou et al. (1980), which reported a significant delay in ossification in rats exposed to 10 mg Cd/kg/day.

The animal studies identify several sensitive targets of toxicity following intermediate-duration exposure to cadmium; these include skeletal mineralization in young female rats exposed for at least 3 months to 0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c), decreased glomerular filtration in young rats exposed during gestation to maternal doses of 0.5 mg Cd/kg/day (Jacquillet et al. 2007), and neurodevelopmental effects following gestational exposure to 0.04 mg Cd/kg/day (Baranski et al. 1983). Although the Baranski et al. (1983) study reported the lowest

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LOAEL, it was not selected as the principal study for derivation of an intermediate-duration MRL. For locomotor activity, a significant decrease in activity was observed in female offspring exposed to 0.04, 0.4, and 4 mg Cd/kg/day, as compared to controls; however, no significant differences were found between the cadmium groups despite the 100-fold difference in doses. Locomotor activity was also decreased in males exposed to 0.4 or 4 mg Cd/kg/day. For the rotorod test, a significant decrease in the length of time the rat stayed on the rotorod was observed in males exposed to 0.04 and 0.4 mg Cd/kg/day, but not to 4 mg Cd/kg/day and in females exposed to 0.4 and 4 mg Cd/kg/day; no differences between the cadmium groups were observed in the males and females. The results were not well described and the investigators did not explain the lack of dose-response of the effects or the discrepancy between genders.

The skeletal effects observed in young rats exposed to cadmium during the period of rapid skeletal growth and mineralization was selected as the critical effect. The Brzóska and associate study (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2005a, 2005c) was selected as the principal study. In this study, groups of 40 3-week-old female Wistar rats were exposed to 0, 1, 5, or 50 mg Cd/L as cadmium chloride in drinking water for 12 months. The investigators noted that cadmium intakes were 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day in the 1, 5, and 50 mg/L groups, respectively. Using cadmium intake data presented in a figure, cadmium intakes of 0.2, 0.5, and 4 mg Cd/kg/day were estimated. Bone mineral density, bone mineral concentration, and mineralization area of the lumbar spine, femur, and total skeleton (bone mineral density only) were assessed after 3, 6, 9, or 12 months of exposure. The mechanical properties of the femur and tibia were evaluated after 12 months of exposure. Markers for bone resorption (urinary and serum levels of C-terminal cross-linking telopeptide of type I collagen [CTX]) and bone formation (serum osteocalcin, total alkaline phosphatase, and cortical bone and trabecular bone alkaline phosphatase), and serum and urinary levels of calcium were also measured at 3, 6, 9, and 12 months.

No significant alterations in body weight gain or food and water consumption were observed. Significant decreases in total skeletal bone mineral density was observed at ≥ 0.2 mg Cd/kg/day; the decrease was significant after 3 months in the 4 mg Cd/kg/day group, after 6 months in the 0.5 mg Cd/kg/day group, and after 9 months in the 0.2 mg Cd/kg/day group. Significant decreases in whole tibia and diaphysis bone mineral density were observed at ≥ 0.2 mg Cd/kg/day after 12 months of exposure. At 0.2 mg Cd/kg/day, bone mineral density was decreased at the proximal and distal ends of the femur after 6 months of exposure; diaphysis bone mineral density was not affected. At 0.5 mg Cd/kg/day, bone mineral density was decreased at the femur proximal and distal ends after 3 months of exposure and diaphysis bone mineral density after 6 months of exposure. At 4 mg Cd/kg/day decreases in femoral

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proximal, distal, and diaphysis bone mineral density were decreased after 3 months of exposure. Similarly, bone mineral density was significantly decreased in the lumbar spine in the 0.2 and 0.5 mg Cd/kg/day groups beginning at 6 months and at 3 months in the 4 mg Cd/kg/day group. Significant decreases in the mineralization area were observed in the femur and lumbar spine of rats exposed to 4 mg Cd/kg/day; lumbar spine bone mineral area was also affected at 0.5 mg Cd/kg/day. Significant decreases in tibia weight and length were observed at 4 mg Cd/kg/day. In tests of the mechanical properties of the tibia diaphysis, significant alterations in ultimate load, yield load, and displacement at load were observed at ≥ 0.2 mg Cd/kg/day; work to fracture was also significantly altered at 4 mg Cd/kg/day. In the mechanical properties compression tests of the tibia, significant alterations were observed in ultimate load, ultimate load, and stiffness at 0.2 mg Cd/kg/day; displacement at yield and work to fracture at ≥ 0.5 mg Cd/kg/day; and displacement at ultimate at 4 mg Cd/kg/day. Multiple regression analysis showed that the cadmium-induced weakness in bone mechanical properties of the tibia was primarily due to its effects on bone composition, particularly the non-organic components, organic components, and the ratio of ash weight to organic weight. The mechanical properties of the femur were strongly influenced by the bone mineral density (at the whole bone and diaphysis). A significant decrease in femur length was observed at 6 months of exposure to ≥ 0.2 mg Cd/kg/day; however, decreases in length were not observed at other time points in the 0.2 or 0.5 mg Cd/kg/day groups. Femur weight was significantly decreased at 4 mg Cd/kg/day. In tests of mechanical properties of the femur (neck and distal portions), decreases in yield load, ultimate load, displacement at ultimate, work to fracture (neck only), and stiffness (distal only) were observed at ≥ 0.2 mg Cd/kg/day. For the femoral diaphysis, significant alterations were observed for yield load, displacement at yield, and stiffness at ≥ 0.2 mg Cd/kg/day. Significant decreases in osteocalcin concentrations were observed in all cadmium groups during the first 6 months of exposure, but not during the last 6 months. Decreases in total alkaline phosphatase levels at 4 mg Cd/kg/day, trabecular bone alkaline phosphatase at 0.2 mg Cd/kg/day, and cortical bone alkaline phosphatase at 4 mg Cd/kg/day were observed. CTX was decreased at ≥ 0.2 mg Cd/kg/day. Total urinary calcium and fractional excretion of calcium were increased at ≥ 0.2 mg Cd/kg/day.

At the lowest dose tested, 0.2 mg Cd/kg/day, a number of skeletal alterations were observed including decreases in bone mineral density in the lumbar spine, femur, and tibia, alterations in the mechanical properties of the femur and tibia, decreases in osteocalcin levels, decreases in trabecular bone alkaline phosphatase, and decreases in CTX. Of these skeletal end points, the decrease in bone mineral density was selected as the critical effect because Brzóska et al. (2005a, 2005c) demonstrated that the bone mineral density was a stronger predictor of femur and tibia strength and the risk of fractures. As discussed in greater detail in Appendix A, available continuous models in the EPA Benchmark Dose

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Software (version 1.4.1c) were fit to data for changes in bone mineral density of the femur and lumbar spine in female rats resulting from exposure to cadmium in the drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). The benchmark dose (BMD) and the 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control. The BMDL_{sd1} derived from the best fitting models for each dataset ranged from 0.05 to 0.17 mg Cd/kg/day. The BMDL_{sd1} of 0.05 mg Cd/kg/day estimated from the 9-month lumbar spine data set was selected as the point of departure for the MRL. In young female rats, the process of intense bone formation occurs during the first 7 months of life (the first 6 months of exposure in this study); thereafter, the increase in bone mineral density slows. In the lumbar spine of the control group, the changes in bone mineral density at 3–6 months, 6–9 months, and 9–12 months were 15, 4, and 1%, respectively. Thus, the 9-month data may best reflect the effect of cadmium on bone mineral density during the period of rapid skeletal growth. The lumbar spine data was selected over the femur data set because trabecular bone, which is abundant in the spine, appears to be more susceptible to cadmium toxicity than cortical bone. The BMDL_{sd1} was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an intermediate-duration oral MRL of 0.5 µg Cd/kg/day.

Chronic-Duration Oral MRL

- An MRL of 0.1 µg/kg/day has been derived for chronic-duration oral exposure (≥1 year) to cadmium.

The database examining the chronic toxicity of cadmium following oral exposure is extensive. Although there are some chronic studies in animals, the majority of the studies in the chronic database examine the relationship between urinary cadmium levels (or cumulative cadmium intake) and adverse health effects in the general population or in populations living in cadmium polluted areas. A variety of health effects have been observed including skeletal defects (osteoporosis, increased bone fractures, decreased bone mineral density), kidney dysfunction, and alterations in reproductive hormone levels. These environmental exposure studies strongly support the identification of bone and kidney as the most sensitive targets of chronic cadmium toxicity.

Bone effects, particularly osteomalacia and/or osteoporosis and increased bone fractures, were first reported in Japanese women living in areas with heavy cadmium contamination. Chronic cadmium exposure has been shown to play a role in this disorder, referred to as Itai-Itai disease; however, other factors such as multiple pregnancies, poor nutrition (low calories, calcium, protein, vitamin D, and iron intakes), and low zinc levels in food also play important roles in the etiology. Although a conclusive role

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of cadmium in Itai-Itai has not been established, several other studies have found bone defects. Observed bone effects include increased risk of bone fractures in postmenopausal women with urinary cadmium levels of $>1 \mu\text{g/day}$ (approximately $>0.7 \mu\text{g Cd/g creatinine}$; Staessen et al. 1999), individuals (>50 years of age) with urinary cadmium levels of $>2 \mu\text{g/g creatinine}$ (Alfvén et al. 2004), and men and women (>40 years of age) with urinary cadmium levels of 9.20 and 12.86 $\mu\text{g/g creatinine}$, respectively (Wang et al. 2003); increased risk of osteoporosis in men (>60 years of age) with urinary cadmium levels of $\geq 1.5 \mu\text{g/g creatinine}$ (Alfvén et al. 2000), in males and females with urinary cadmium levels of $\geq 10 \mu\text{g/g creatinine}$ (Jin et al. 2004b), in males and females (>40 years of age) with urinary cadmium levels of 9.20 and 12.86 $\mu\text{g/g creatinine}$, respectively (Wang et al. 2003), and women with renal tubular damage (urinary NAG $\geq 12 \text{ IU/g creatinine}$) (Chen et al. 2011); and decreased bone mineral density in women with urinary cadmium levels of $>0.6 \mu\text{g/g creatinine}$ (Schutte et al. 2008), postmenopausal women with urinary cadmium levels of $>20 \mu\text{g/g creatinine}$ (Nordberg et al. 2002), postmenopausal women with median urinary cadmium levels of 1.1 $\mu\text{g/g creatinine}$ (Engström et al. 2009), and men with urinary cadmium levels of $\geq 2 \mu\text{g/g creatinine}$ (Trzcinka-Ochocka et al. 2010).

Evidence of renal dysfunction in environmentally exposed populations include increases in deaths from renal dysfunction in residents living in cadmium polluted areas of Japan (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006), increases in renal replacement therapy which is indicative of severe renal dysfunction (Hellström et al. 2001), and increases in the excretion of biomarkers of renal dysfunction in association with increased cadmium intake, increased renal cadmium concentrations, increased blood cadmium levels, and/or increased urinary cadmium concentrations (Bandara et al. 2010; Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Ferraro et al. 2010; Hayano et al. 1996; Honda et al. 2010; Horiguchi et al. 2004, 2010; Hwangbo et al. 2011; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a, 2009b; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). The urinary excretion of several biomarkers have been shown to increase due to cadmium-related alterations in kidney function; these biomarkers include low molecular weight proteins (e.g., β_2 -microglobulin, pHc, retinol binding protein), intracellular tubular enzymes (e.g., NAG), amino acids, high molecular weight proteins (e.g., albumin), metallothionein, and electrolytes (e.g., potassium, sodium, calcium). Although the more severe renal effects have been observed in populations living in highly contaminated areas (e.g., decreased glomerular filtration rate), alterations in the above biomarkers

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have been observed in areas not considered to be cadmium polluted. Alterations in these biomarker levels appear to be the most sensitive indicator of cadmium toxicity. Many of the studies examining biomarkers have reported significant correlations between urinary cadmium levels and biomarker levels. However, these correlations do not provide insight into exposure levels associated with renal dysfunction. In this MRL analysis, attention was given to dose-response studies examining the derived quantitative relationships between cadmium exposure and the prevalence of abnormal biomarker levels. As discussed in the inhalation MRL section, a 10% increase in the prevalence of abnormal biomarker levels (particularly β 2-microglobulin, pHc, or retinol binding protein) in association with increasing cadmium exposure is generally considered to be indicative of cadmium-associated renal dysfunction in populations. However, when examining the prevalence of abnormal levels, careful consideration should be given to the response criterion (cut-off level) used in the study. A wide range of cut-off levels have been used in the environmental exposure studies. For β 2-microglobulin, the most commonly used biomarker, the cut-off values ranged from 283 to 1,129 μ g/g creatinine. A summary of environmental studies finding significant dose-response associations between urinary cadmium (or cumulative cadmium intake) and the prevalence of abnormal levels of urinary biomarkers of renal dysfunction is presented in [Table 2-1](#). The adverse effect levels range from urinary cadmium levels of 1 μ g/g creatinine (Järup et al. 2000) to 9.51 μ g/g creatinine (Jin et al. 2004a).

The adverse effect levels for renal effects were similar to those observed for skeletal effects. Because the renal effects database is stronger, it was used for derivation of a chronic-duration oral MRL for cadmium. Several approaches were considered for derivation of the MRL: (1) NOAEL/LOAEL approach using a single environmental exposure study finding an increased prevalence of abnormal renal effect biomarker levels, (2) selection of a point of departure from a published benchmark dose analysis, or (3) selection of a point of departure based on an analysis of the dose-response functions from a number of environmental exposure studies.

In the first approach, all studies in which individual internal doses for subjects were estimated based on urinary cadmium were considered. The Järup et al. (2000) study is selected as the principal study because it identified the lowest adverse effect level ([Table 2-1](#)). In this study, 1,021 individuals living near a nickel-cadmium battery factory (n=799) or employed at the factory (n=222) were examined. The mean urinary cadmium concentrations were 0.81 μ g/g creatinine in men and 0.65 μ g/g creatinine in women. A significant association was found between urinary cadmium concentrations and urinary pHc levels, after adjustment for age; the association remained statistically significant after removal of the cadmium workers from the analysis. The investigators estimated that a urinary cadmium level of 1 μ g/g creatinine

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Table 2-1. Summary of Human Studies Finding Dose-Response Relationships Between Biomarkers of Renal Dysfunction and Cadmium Exposure

Population	Effect biomarker	Response criterion	Adverse effect level (urinary cadmium)	Reference
General population (Japan)	Total prt	157.4 µg/g creat. (M) 158.5 µg/g creat. (F)	2.4 µg/g creat. ^a	Suwazono et al. 2006
	β2M	507 µg/g creat. (M) 400 µg/g creat. (F)		
	NAG	8.2 µg/g creat. (M) 8.5 µg/g creat. (F)		
General population (Belgium)	β2M	283 µg/24 hours	1.92 µg/g creat. ^b	Buchet et al. 1990
	RBP	338 µg/24 hours		
	NAG	3-6 IU/24 hours		
	amino acid	357 mg α-N/24 hours		
	calcium	4-9 mmol/24 hours		
Residents in cadmium-polluted area (China)	β2M	355 µg/g creat. (M <45 years) >2,500 µg/g creat. (M ≥45 years) 500 µg/g creat. (F)	4–7.99 µg/g creat. ^c	Cai et al. 1998
Residents in cadmium-polluted area (China)	β2M	300 µg/g creat.	≥5 µg/g creat.	Jin et al. 2002
	RBP	300 µg/g creat.		
	albumin	15 mg/g creat.		
Residents in cadmium-polluted area (China)	β2M	800 µg/g creat.	9.51 µg/g creat.	Jin et al. 2004a
	NAG	15 U/g creat.		
	albumin	20 mg/g creat.		
Residents in cadmium-polluted area (China)	β2M	800 µg/g creat.	2–4 µg/g creat. ^c	Nordberg et al. 1997
Residents in cadmium-polluted area (Japan)	β2M	1,000 µg/g creat.	6.9 µg/g creat.	Cai et al. 2001
Residents in cadmium-polluted area (Japan)	β2M	1,000 µg/g creat. (M,F)	Cadmium intake: 150 µg/day	Nogawa et al. 1989; Kido and Nogawa 1993
Residents in cadmium-polluted area (Japan)	β2M	1,129 µg/g creat. (M) 1,059 µg/g creat. (F)	4–4.9 µg/g creat. ^c	Ishizaki et al. 1989; Hayano et al. 1996

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Table 2-1. Summary of Human Studies Finding Dose-Response Relationships Between Biomarkers of Renal Dysfunction and Cadmium Exposure

Population	Effect biomarker	Response criterion	Adverse effect level (urinary cadmium)	Reference
Residents in cadmium-polluted area (Thailand)	β2M	400 µg/g creat.	6–10 µg/g creat.	Teeyakasem et al. 2007
Residents in cadmium-polluted area (includes occupationally exposed subjects (Sweden)	pHC	7.1 mg/g creat. (M) 5.3 mg/g creat. (F)	1 µg/g creat. ^d	Järup et al. 2000

^aMean urinary cadmium level

^b>10% prevalence of abnormal β2-microglobulin, retinal binding protein, amino acid, and calcium values at 3.05, 2.87, 2.74, 4.29, or 1.92 µg/24 hours, respectively.

^cUrinary cadmium level associated with an approximate doubling of prevalence of abnormal β2-microglobulin levels

^dThe European Chemicals Bureau (2007) recalculated this value (using raw data from Järup et al. 2000) to account for differences in age of the reference population and study population; based on these recalculations, a doubling of the probability of abnormal pHC values would occur at 2.62 µg/g creatinine for the total population and a 0.5 µg/g creatinine for the environmentally exposed population.

AAP = alanine aminopeptidase; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; NAG = N-acetyl-β-glucosaminidase; pHC = human complex-forming glycoprotein, also referred to as α1M; RBP = retinol binding protein

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would be associated with a 10% increase in the prevalence of abnormal pHC levels above background prevalence (approximately a 10% added risk). However, the European Chemicals Bureau (2007) recalculated the probability of HC proteinuria because the reference population and the study population were not matched for age (40 versus 53 years, respectively). They estimated that the probability of HC proteinuria (13%) would be twice as high as the reference population at a urinary cadmium concentration of 0.5 µg/g creatinine.

The second approach involves the evaluation of eight published benchmark dose analyses. The benchmark doses and the lower 95% confidence interval of the benchmark dose (BMDL) for low molecular weight proteinuria are presented in Table 2-2 (benchmark doses and BMDLs for all effect parameters are presented in Table 3-8 in the toxicological profile). The BMDL values corresponding to a 10% increase in the prevalence of low molecular weight proteinuria above background (excess risk) ranged from 0.7 µg/g creatinine (Uno et al. 2005) to 9.9 µg/g creatinine (Kobayashi et al. 2006). Both studies examined populations living in non-cadmium polluted areas of Japan and used β2-microglobulin as the effect biomarker. The large difference in cut-off values (233 versus 784 µg/g creatinine) likely contributed to the order of magnitude difference in BMDLs. The BMDL₁₀ of 0.7 µg/g creatinine is supported by the Suwazono et al. (2006) benchmark dose analysis, which found a similar BMDL₁₀ (0.81 µg/g creatinine) using pHC as the effect biomarker. The Uno et al. (2005) study examined 410 men and 418 women (aged 40–59 years) living in three areas of Japan without any known environmental cadmium pollution. Mean urinary cadmium concentrations were 1.3 and 1.6 µg/g creatinine in men and women, respectively. Cut-off levels for β2-microglobulin were 233 and 274 µg/g creatinine in males and females; these values represent the 84% upper limit values calculated from the target population assuming a log normal distribution.

The third approach involved a meta-analysis of selected environmental exposure dose-response studies. Studies were selected for inclusion in this analysis based on the following qualitative criteria: (1) the study measured urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of low molecular weight (LMW) proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. No attempt was made to weight selected studies for quality, statistical power, or statistical uncertainty in dose-response parameters. Studies using a cut-off

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Table 2-2. Selected Benchmark Dose Estimations of Urinary Cadmium Levels Associated with Increases in the Prevalence of Low Molecular Weight Proteinuria

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Sweden)	pHC	6.8 mg/g creat. (95% cut-off) ^a	Profile likelihood method	0.63 (F)	0.49 (F)	1.05 (F)	0.81 (F)	Suwazono et al. 2006
Residents in cadmium-polluted and non-polluted areas (Japan)	β2M	507 μg/g creat. (M)	Quantal linear model	1.5 (M)	1.2 (M)	3.1 (M)	2.5 (M)	Shimizu et al. 2006
		400 μg/g creat. (F)		1.4 (F)	1.1 (F)	2.9 (F)	2.3 (F)	
		994 μg/g creat. (M)		2.3 (M)	1.8 (M)	4.7 (M)	3.7 (M)	
		784 μg/g creat. (F)		1.7 (F)	1.4 (F)	3.5 (F)	2.9 (F)	
Residents in cadmium-polluted ^d and nonpolluted areas (Japan)	β2M	915.5 μg/g creat. (M)	Profile likelihood method	4.0 (M)	3.5 (M)	Not calculated		Suwazono et al. 2011b
		897.1 μg/g creat. (F)		4.0 (F)	(3.7)F)			
General population (Japan)	β2M	507 μg/g creat. (M)	Log-logistic model	2.9 (M)	2.4 (M)	5.0 (M)	4.0 (M)	Kobayashi et al. 2006
		400 μg/g creat. (F)		3.8 (F)	3.3 (F)	6.6 (F)	5.5 (F)	
		994 μg/g creat. (M)		6.4 (M)	4.5 (M)	10.2 (M)	7.1 (M)	
		784 μg/g creat. (F)		8.7 (F)	7.3 (F)	12.0 (F)	9.9 (F)	
General population (Japan)	β2M	492 μg/g creat. (M)	Multiple logistic model	3.0 (M)	2.7 (M)	5.0 (M)	4.6 (M)	Kobayashi et al. 2008a
		407 μg/g creat. (F)		3.4 (F)	3.2 (F)	5.7 (F)	5.4 (F)	
		965 μg/g creat. (M)		4.9 (M)	4.5 (M)	7.4 (M)	6.8 (M)	
		798 μg/g creat. (F)		5.9 (F)	5.6 (F)	8.6 (F)	8.1 (F)	
General population (Japan)	β2M	708 μg/g creat. (M)	Profile likelihood method	3.4 (M)	2.6 (M)	Not calculated		Suwazono et al. 2011c
		415 μg/g creat. (F)		1.7 (F)	1.4 (F)			

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Table 2-2. Selected Benchmark Dose Estimations of Urinary Cadmium Levels Associated with Increases in the Prevalence of Low Molecular Weight Proteinuria

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Japan)	β 2M	233 μ g/g creat. (M) 274 μ g/g creat. (F) (84% cut-off) ^k	Quantal linear model	0.5 (M) 0.9 (F)	0.4 (M) 0.8 (F)	1.0 (M) 1.8 (F)	0.7 (M) 1.3 (F)	Uno et al. 2005
Residents in cadmium highly, or moderately polluted area (China)	β 2M	800 μ g/g creat. (95% cut-off) ^l	Quantal linear	5.86 (M) 9.98 (F)	4.74 (M) 8.47 (F)			Jin et al. 2004c
	RBP	0.300 mg/g creat. (95% cut-off) ^l	logistic regression model	5.99 (M) 9.03 (F)	4.87 (M) 7.63 (F)			

^a95th percentile of effect biomarkers on the “hypothetical” control distribution at a urinary cadmium level of zero.

^b84% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.

^c95% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.

^dSame population of residents living in polluted area as Shimizu et al. (2006).

^e95th percentile calculated by benchmark model at no cadmium exposure (urinary cadmium equal to zero), adjusted to mean age.

^f84% upper limit value of the target population of people who have not smoked.

^g95% upper limit value of the target population of people who have not smoked.

^h84th percentile level in subjects from nonpolluted areas.

ⁱ97.5th percentile level in subjects from nonpolluted areas.

^j95th percentile calculated by benchmark model at no cadmium exposure (urinary cadmium equal to zero), adjusted to mean age.

^k84% upper limit value of the target population.

^l95% upper limit value from a control group 98 males and 155 females living in a cadmium nonpolluted area.

BMD = benchmark dose; BMDL = benchmark dose low; BMR = benchmark response; β 2M = β 2-microglobulin; creat. = creatinine; F = female; M = male; NAG = *N*-acetyl- β -D-glucosaminidase; NAG-B = *N*-acetyl- β -D-glucosaminidase's isoform B; RBP = retinol binding protein

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value for $\beta 2$ -microglobulin of $\geq 1,000$ $\mu\text{g/g}$ creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary $\beta 2$ -microglobulin levels of 1,000–10,000 $\mu\text{g/g}$ creatinine were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in GFR. Additionally, an attempt was made to avoid using multiple analyses of the same study population.

The individual dose-response functions from each study were implemented to arrive at estimates of the internal dose (urinary cadmium expressed as $\mu\text{g/g}$ creatinine) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). Estimates were derived from the seven environmental exposure studies listed in Table 2-3. When available, male and female data were treated separately; thus, 11 dose-response relationships were analyzed. For studies that did not report the UCD_{10} , the value was estimated by iteration of the reported dose response relationship for varying values of urinary cadmium, until an excess risk of 10% was achieved:

$$ER = \frac{P(d) - P(0)}{1 - P(0)}$$

where ER is the excess risk, $P(d)$ is the probability of low molecular weight proteinuria associated with a given internal (i.e., urinary cadmium) dose, and $P(0)$ is the background probability (i.e., the probability predicted by the dose-response model when urinary cadmium was zero). For studies that reported the dose-response relationship graphically, but did not report the actual dose-response function, a function was derived by least squares fitting based on data from a digitization of the graphic.

Aggregate UCD_{10} estimates and the estimates stratified by location (i.e., Europe, Japan, China) are presented in Figure 2-2. The lowest UCD_{10} (1.34 $\mu\text{g/g}$ creatinine) was estimated from the European database and the 95% lower confidence limit on this UCD_{10} (UCDL_{10}) of 0.5 $\mu\text{g/g}$ creatinine was considered as a potential point of departure for the MRL.

Points of departure selected using the three different approaches are similar: 0.5 $\mu\text{g/g}$ creatinine from the Järup et al. (2000) study (using the European Chemicals Bureau 2007 recalculation), 0.7 $\mu\text{g/g}$ creatinine from the Uno et al. (2005) benchmark dose analysis, and 0.5 $\mu\text{g/g}$ creatinine from the dose-response analysis. The third approach (meta-analysis of environmental exposure studies) was selected for the derivation of the MRL because it uses the whole dose-response curves from several studies rather than data from a single study.

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Table 2-3. Selected Studies of Dose-Response Relationship for Cadmium-Induced Low Molecular Weight Proteinuria

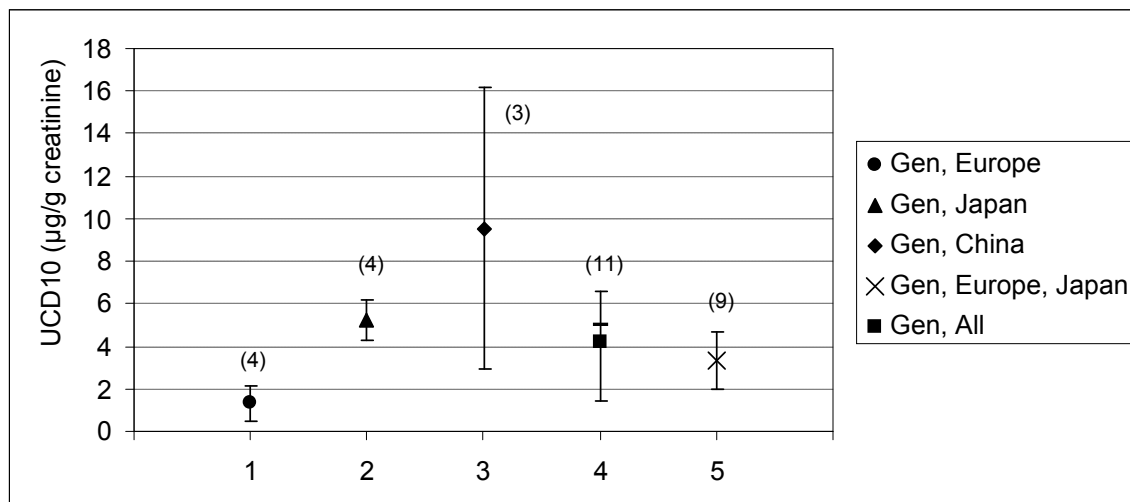
Reference	Population	Number	Effect biomarker	Response criterion	Dose-response model	UCD ₁₀ (µg/g creat.)
Buchet et al. 1990	General population (Belgium)	1,699 M 2,080 F	β2M	283 µg/24 hours	Logistic ^a	2.51 M 1.44 F
Suwazono et al. 2006	General population (Sweden)	790 F	pHC	3.6 U/g creat.	Logistic	0.81
Järup et al. 2000	Residents in cadmium polluted area (Sweden)	1,465 M,F	pHC	7.1 mg/g creat. M 5.3 mg/g creat. F	Logistic	0.6
Kobayashi et al. 2006	General population (Japan)	1,114 M 1,664 F	β2M	507 µg/g creat. M 400 µg/g creat. F	Log-logistic	5.0 M 6.6 F
Shimizu et al. 2006	Residents in cadmium polluted and non-polluted areas (Japan)	1,865 M 1,527 F	β2M	507 µg/g creat. M 400 µg/g creat. F	Log-logistic	5.1 M 4.2 F
Jin et al. 2004c	Residents in cadmium polluted or non-polluted area (China)	790 M,F	β2M	800 µg/g creat.	Logistic	9.5 M 15.4 F
Wu et al. 2001	Residents in cadmium polluted area (China)	247 M,F	β2M	800 µg/g creat. M 900 µg/g creat. F	Linear ^b	3.75

^aDigitized from Figure 2 in Lauwerys et al. 1991^bDigitized from Figure 2 in Wu et al. 2001

β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; pHC = human complex-forming glycoprotein (also referred to as α1-microglobulin); UCD₁₀ = urinary cadmium level corresponding to a probability of 10% excess risk of low molecular weight proteinuria

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Figure 2-2. Estimates of the UCD₁₀ from Environmental Exposure Dose-Response Studies*



*Estimates of urinary cadmium concentrations (µg/g creatinine) associated with a 10% excess risk of urinary β₂-microglobulin (UCD₁₀) using data from European, Japanese, and Chinese studies. For the aggregate of studies (plot #4), the mean (-), median (•), and 95% confidence intervals (CI) on the median are shown. All other plots show the mean and 95% CI on the mean. Numbers in parenthesis are the number of estimates of the UCD₁₀.

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The UC_{DL10} of 0.5 µg/g creatinine was transformed into estimates of chronic cadmium intake (expressed as µg Cd/kg/day) that would result in the UC_{DL10} at age 55 (approximate age of peak cadmium concentration in the renal cortex associated with a constant chronic intake; Figure 2-3). The dose transformations were achieved by simulation using a modification of the Nordberg-Kjellström model (Kjellström and Nordberg 1978). The following modifications (Choudhury et al. 2001; Diamond et al. 2003) were made to the model: (1) the equations describing intercompartmental transfers of cadmium were implemented as differential equations in Advanced Computer Simulation Language (acslXtreme, version 2.4.0.9); (2) growth algorithms for males and females and corresponding organ weights (O'Flaherty 1993) were used to calculate age-specific cadmium concentrations from tissue cadmium masses; (3) the cadmium concentration in renal cortex (RC, µg/g) was calculated as follows:

$$RC = 1.5 \cdot \frac{K}{KW}$$

where K is the age-specific renal cadmium burden (µg) and KW is the age-specific kidney wet weight (g) (Friberg et al. 1974).

(4) the rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur}; and (5) absorption of ingested cadmium was assumed to be 5% in males and 10% in females. The rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was estimated from the relationship between LBM (kg) and Cr_{ur}:

$$LBM = 27.2 \cdot Cr_{ur} + 8.58$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976). Lean body mass was estimated as follows (ICRP 1981):

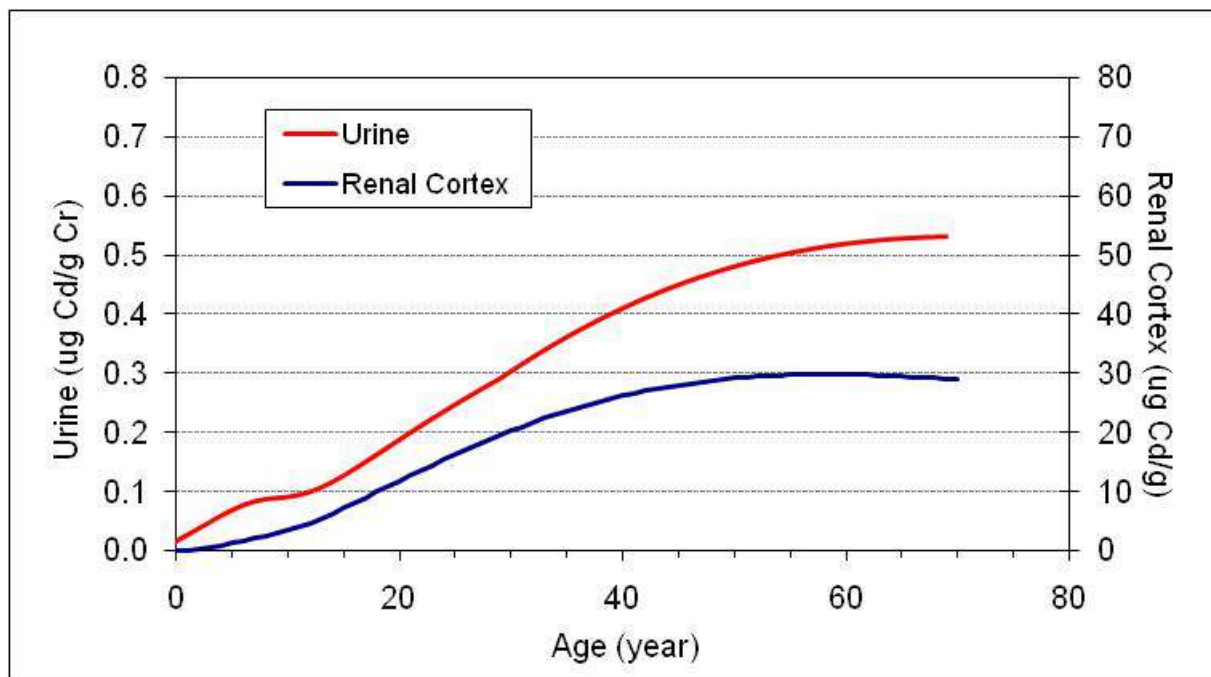
$$LBM = BW \cdot 0.85, \text{adult females}$$

$$LBM = BW \cdot 0.88, \text{adult males}$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively.

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Figure 2-3. Urinary Cadmium ($\mu\text{g/g}$ creatinine) and Renal Cortex Cadmium Concentration ($\mu\text{g/g}$ wet tissue) Predicted by the Cadmium Pharmacokinetic Model*



*Shown is a simulation of peak renal cadmium concentration (at age 55) in females based on a chronic intake of $0.33 \mu\text{g Cd/kg/day}$.

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Dose units expressed as cadmium intake ($\mu\text{g/kg/day}$), urinary cadmium excretion ($\mu\text{g/g creatinine}$), or kidney tissue cadmium ($\mu\text{g/g cortex}$) were interconverted by iterative pharmacokinetic model simulations of constant intakes for the life-time to age 55 years, the age at which renal cortex cadmium concentrations are predicted to reach their peak when the rate of intake ($\mu\text{g/kg/day}$) is constant.

The dietary cadmium intakes which would result in urinary cadmium levels of 1.34 and 0.5 $\mu\text{g/g creatinine}$ (UCD_{10} and UCDL_{10}) are 0.97 and 0.33 $\mu\text{g/kg/day}$ in females and 2.24 and 0.70 $\mu\text{g/kg/day}$ in males. The dietary concentration associated with the UCDL_{10} in females (0.33 $\mu\text{g/kg/day}$) was divided by an uncertainty factor of 3 for human variability resulting in a chronic-duration oral MRL of 0.1 $\mu\text{g/kg/day}$ ($1 \times 10^{-4} \text{ mg Cd/kg/day}$). The UCD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations; however, there is concern that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990) and diabetics were excluded from a number of the human studies, and thus, an uncertainty factor of 3 was used.

The urinary cadmium point of departure used as the basis of the MRL (0.5 $\mu\text{g/g creatinine}$) is approximately 2-fold higher than the geometric mean urinary cadmium concentrations in the United States, which is 0.247 $\mu\text{g/g creatinine}$ for adults 20 years and older (CDC 2011). The MRL of 0.1 $\mu\text{g/kg/day}$ is lower than the estimated age-weighted cadmium intake of 0.3 $\mu\text{g/kg/day}$ (estimated from data in Choudhury et al. 2001). Because this intake is derived from the cadmium dietary exposure model which estimates food cadmium concentrations from national survey data and food consumption patterns, it should not be considered a precise value. A better comparison would be between the mean urinary cadmium concentration in adults living in the United States (0.247 $\mu\text{g/g creatinine}$) and the MRL expressed as a urinary cadmium concentration (0.2 $\mu\text{g/g creatinine}$).

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cadmium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

The form of cadmium and the route of exposure can greatly affect the absorption and distribution of cadmium to various target sites, and therefore, the concentration at the target site and the severity of the observed effect. The mechanism of action, however, involves the cadmium cation's effect on the target site, and the cation is the same regardless of the anionic species. For inhaled cadmium compounds, the size of the cadmium particle (i.e., fume or aerosol) can also affect the absorption and distribution. For oral exposures, cadmium chloride is most often tested in animal studies because of its high water solubility and the resulting high concentrations of cadmium delivered to target sites. Studies on cadmium bound to metallothionein are also of interest because cadmium-metallothionein complexes may have different toxic profiles and are found in relatively high levels in organ meats (e.g., liver and kidney). Cadmium oxide and cadmium carbonate, which are relatively insoluble in water (but may dissolve at gastric pH), appear to be similar in absorption and toxicity to soluble cadmium. There are fewer studies available on other forms of cadmium including insoluble forms in water such as cadmium sulfide (a yellow pigment) and cadmium selenium sulfide (a red pigment), and a soluble form, cadmium sulfate, which is less soluble in a closed air system where there is a limited amount of dissolved carbon dioxide. Chapter 4 lists the chemical and physical properties of several cadmium compounds.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

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Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of cadmium are indicated in [Tables 3-1](#) and [3-6](#) and [Figures 3-1](#) and [3-2](#). Because cancer effects could occur at lower exposure levels, [Figure 3-1](#) also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

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3.2.1 Inhalation Exposure

The information in this section on health effects of inhalation exposure to cadmium in humans is derived from studies of workers exposed to cadmium fume or dusts in industries such as smelting, battery manufacturing, soldering, and pigment production. Adverse effects of human exposure to cadmium were first established among workers in a cadmium battery factory (Friberg 1950). Workers are exposed occupationally to cadmium primarily by inhalation of fumes or dust. Some gastrointestinal tract exposure may also occur when dust is removed from the lungs by mucociliary clearance and subsequently swallowed, or by ingestion of dust on hands, cigarettes, or food (Adamsson et al. 1979). In experiments with animals, some ingestion may also occur from inhalation exposures by mucociliary clearance or from animal grooming. The primary form of cadmium in occupational exposures is cadmium oxide. Experimental studies in laboratory animals have used cadmium oxide, cadmium chloride, and occasionally other forms of cadmium such as cadmium sulfide and cadmium sulfate. In general, the different forms of cadmium have similar toxicological effects by the inhalation route, although quantitative differences may exist from different absorption and distribution characteristics, particularly for the less soluble cadmium pigments such as cadmium sulfide and cadmium selenium sulfide (Buckley and Bassett 1987b; Klimisch 1993; Oldiges and Glaser 1986; Oldiges et al. 1989; Rusch et al. 1986).

Smokers inhale cadmium, but studies of cadmium exposure in the general population are considered in Section 3.2.2 because the primary route of exposure for the general population is through the diet. Also, the many other toxic compounds in cigarette smoke make it difficult to attribute specific adverse effects of smoking to the inhalation of cadmium.

3.2.1.1 Death

Numerous studies have shown that acute inhalation exposure to cadmium can cause death in humans and animals. In humans, several fatal inhalation exposures have occurred in occupational accidents. During the acute exposure, the general symptoms are relatively mild but, within a few days following exposure, severe pulmonary edema and chemical pneumonitis develop, leading to death due to respiratory failure (Beton et al. 1966; Lucas et al. 1980; Patwardhan and Finckh 1976; Seidal et al. 1993). The cadmium concentration in air was not measured in these cases of accidental death in humans. However, the lung concentrations of cadmium in the men who died from these accidental acute exposures were measured. In micrograms of cadmium per gram wet weight (w/w) of lung tissue ($\mu\text{g/g}$), Patwardhan and Finckh (1976) reported 1.5 $\mu\text{g/g}$, Beton et al. (1966) reported 2.5 $\mu\text{g/g}$, Barrett et al. (1947) reported 3.5 $\mu\text{g/g}$, and Lucas et al. (1980) reported 4.7 $\mu\text{g/g}$. Based upon estimates of the percentage of inhaled cadmium fume

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that would be retained in the lungs, Barrett et al. (1947) calculated an exposure of 2,500 minutes \times mg/m³ in air would be fatal to humans. Beton et al. (1966) used a similar technique to estimate that an exposure to cadmium oxide in air of 8.63 mg/m³ for 5 hours led to the fatal deaths of the five workers with cadmium lung burdens of 2.5 μ g/g. The lower lung concentrations reported by Patwardhan and Finckh (1976) prompted Elinder (1986b) to estimate that an exposure of 1–5 mg/m³ for 8 hours could be immediately dangerous. These estimates of air concentrations, however, are based on a number of uncertain assumptions concerning the duration of exposure and the retention of cadmium in the human lung being similar to that found in animal studies (Barrett et al. 1947; Elinder 1986b). No studies on deaths in humans from intermediate inhalation exposures were found. In a study on chronic exposures, Friberg (1950) attributes the deaths of 2 workers to exposure to cadmium dust in the air averaging 6.8 mg Cd/m³ (range 3–15 mg/m³). One worker was 57 years old at death (after 14 years of exposure to the dust) and the other was 60 years old at death (after 25 years of exposure to the dust). A detailed postmortem evaluation for the 60-year-old worker showed the presence of emphysema and the occurrence of hyaline casts in renal tubules, as well as slight nephrotic changes. Pneumonia was the direct cause of death as an acute complication of chronic bronchitis and pulmonary emphysema. The exposure estimate of 6.8 mg Cd/m³ is from only six samples taken in 1946. The conditions in earlier years were thought to be similar, but this exposure value is, at best, a very rough approximation of the actual exposures spanning 34 years.

Acute inhalation of cadmium oxide fumes has also led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the product of the duration of exposure and the concentration of inhaled cadmium (Barrett et al. 1947). The most reliable LC₅₀ (lethal concentration, 50% kill) (at 7 days) established by this study was 500 minute-mg cadmium oxide/m³ for rats, equivalent to a 15-minute exposure to 30 mg Cd/m³ (Barrett et al. 1947). Rusch et al. (1986) demonstrated high mortality rates in the Sprague-Dawley rat from a 2-hour exposure to cadmium fumes at 112 mg Cd/m³ (25 of 32 died within 1 week). A 2-hour exposure to a different form of cadmium, cadmium carbonate, at 132 mg Cd/m³ resulted in considerably lower mortality (3 of 22 died by day 30). No deaths resulted from a 2-hour exposure to cadmium sulfide at 99 mg Cd/m³ or cadmium selenium sulfide (cadmium red pigment) at 97 mg Cd/m³. Grose et al. (1987) reported 2 out of 36 rats died from a 2-hour, nose-only inhalation exposure to only 0.45 mg Cd/m³ of cadmium oxide dusts, but the statistical significance of this low rate of mortality was not reported. A 3-day, 1-hour/day exposure to cadmium chloride aerosol at 61 mg Cd/m³ resulted in the death of 17 of 18 rats exposed (Snider et al. 1973). In another study, no deaths were observed in rats from a cadmium yellow (cadmium sulfide) pigment exposure 6 hours/day for 10 days at 6.29 mg Cd/m³ (Klimisch 1993). Thus, it appears that in acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium

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carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds (Klimisch 1993; Rusch et al. 1986). Rusch et al. (1986) attribute this difference to higher lung absorption and retention times for the more soluble compounds, and greater mucociliary clearance for the less-soluble pigments. Glaser et al. (1986), however, demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water. In hamsters, Henderson et al. (1979) reported that a 30-minute exposure to 10.1 mg Cd/m³ from cadmium chloride resulted in the death of 3 of 30 animals by day 6 postexposure. In rabbits, Friberg (1950) reported an LC₅₀ (by day 14) from a 4-hour exposure to cadmium metal dusts at 28.4 mg Cd/m³. Barrett et al. (1947) also reported LC₅₀ values for cadmium oxide fume of 940 mg Cd/m³ for a 14-minute exposure in the monkey, 46.7 mg/m³ for a 15-minute exposure in the mouse, 204 mg Cd/m³ for a 15-minute exposure in the guinea pig, and 230 mg Cd/m³ for a 15-minute exposure in the dog. However, the authors report that these LC₅₀ values are only approximations because of insufficiencies in the data or the small numbers of animals used.

At longer durations of exposure, lower concentrations cause lethality in rats. Cadmium oxide dust resulted in the deaths of 100% of the females at 1 mg Cd/m³ for 5 hours/day, 5 days/week for 20 weeks, (Baranski and Sitarek 1987), and of 5 of 12 female rats at only 0.105 mg Cd/m³ 22 hours/day, 7 days/week for 63 days (Oldiges and Glaser 1986). Continuous inhalation exposure to cadmium oxide dust at 0.105 mg Cd/m³ (i.e., 24 hours/day) for 63 days resulted in 5 of 12 deaths in female rats (Prigge 1978a). Five of 54 males died from a cadmium chloride exposure to 1.06 mg Cd/m³ for 62 days, 5 days/week, 6 hours/day (Kutzman et al. 1986). Kutzman et al. (1986) determined that the concentration times hours of exposure to produce 50% mortality in rats was 390 mg-hour/m³ (males) and 489 mg-hour/m³ (females). Takenaka et al. (1983) reported that cadmium chloride at 0.0508 mg Cd/m³ 23 hours/day, 7 days/week for 18 months resulted in the death of 5 of 40 male rats.

Oldiges et al. (1989) evaluated the long-term effects in rats of inhaling cadmium as either cadmium chloride, cadmium sulfate, cadmium sulfide, or cadmium oxide. Rats were exposed to aerosols in nearly continuous exposures of 22 hours/day, 7 days/week for 18 months. An observation period of 12 months followed the exposure period. Oldiges et al. (1989) recorded mortality as exceeding 25% of the test animals during the exposure period or 75% of the test animals during the observation period. If either 25 or 75% mortality occurred, the exposure period or the observation period, respectively, was terminated. The results showed that cadmium chloride at 0.030 mg Cd/m³ was lethal to >75% of the male and female rats by 12 months of exposure; cadmium oxide dusts at 0.090 mg Cd/m³ were lethal for >25% of the males by 7 months and 25% of the females by 11 months of exposure; cadmium oxide fume at the

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highest dose of 0.03 mg Cd/m³ did not result in >25% mortality during exposure or 75% during the postexposure period; cadmium sulfate at 0.090 mg Cd/m³ was lethal for >25% of the males during the exposure and for >75% of the females by 14 months following exposure; and cadmium sulfide at 0.090 mg Cd/m³ was not lethal during the exposure period but was lethal to >75% of the males and females by 12 months postexposure. In these chronic studies, cadmium's lethal effects differed among the chemical forms in the following order from most to least toxic: cadmium chloride>cadmium sulfate ≈ cadmium oxide dust>cadmium sulfide, but lethality still occurred from all forms of cadmium. Oldiges and Glaser (1986) report that in their chronic studies and at the doses tested, cadmium toxicity appeared to be more related to the long-term lung retention of the bioavailable amounts of cadmium than to a simple function of solubility in water. Representative LOAEL and LC₅₀ values for lethality in each species and duration category are recorded in [Table 3-1](#) and are plotted in [Figure 3-1](#).

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#).

Respiratory Effects. In humans, inhalation exposure to high levels of cadmium oxide fumes or dust is intensely irritating to respiratory tissue, but symptoms can be delayed. During and immediately after (up to 2 hours) an acute exposure for 5 hours of 8.63 mg/m³, Beton et al. (1966) reported that there were few symptoms of toxicity limited to coughing and slight irritation of the throat and mucosa. From 4 to 10 hours postexposure, influenza-like symptoms began to appear, including cough, tight chest, pain in chest on coughing, dyspnea, malaise, ache, chilling, sweating, shivering, and aching pain in back and limbs. From 8 hours to 7 days postexposure, more advanced stages of pulmonary response included severe dyspnea and wheezing, chest pain and precordial constriction, persistent cough, weakness and malaise, anorexia, nausea, diarrhea, nocturia, abdominal pain, hemoptysis, and prostration. Acute, high-level exposures can be fatal (see Section 3.2.1.1), and those who survive may have impaired lung function for years after a single acute exposure. A 34-year-old worker exposed to cadmium fume from soldering for 1 hour (dose not determined) had persistent impaired lung function when examined 4 years following the exposure (Barnhart and Rosenstock 1984). Initial symptoms were dyspnea, cough, myalgia, and fever. An initial chest X-ray revealed infiltrates. Townshend (1982) reports the case of a male welder who developed acute cadmium pneumonitis from a single exposure (dose not determined). Nine years after the exposure, this worker continued to show signs of progressive pulmonary fibrosis and

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m³)	Serious (mg/m³)		
ACUTE EXPOSURE							
Death							
1	Human	5 hr (occup)			8.63 M (5 male workers died after a 5 hour exposure)	Beton et al. 1966 CdO fume	
2	Rat (NS)	10-15 min			30 (LC50 at 7 days)	Barrett et al. 1947 CdO fume	
3	Rat (Fischer- 344)	6.2 hr/d 5 d/wk 2 wk			8.8 (100% mortality by day 6)	NTP 1995 CdO	
4	Rat (Sprague- Dawley)	2 hr			112 (25/32 died within 1 week)	Rusch et al. 1986 CdO fume	
5	Rat (Sprague- Dawley)	3 d 1 hr/d			61 M (17/18 died within 3 days)	Snider et al. 1973 CdCl2	
6	Mouse (B6C3F1)	6.2 hr/d 5 d/wk 2 wk			8.8 (100% mortality by day 7)	NTP 1995 CdO	
7	Rabbit (NS)	4 hr			28.4 (LC50 at 14 days)	Friberg 1950 Cd metal dust	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure ^a Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m³)	Serious (mg/m³)		
Systemic							
8	Rat (Long- Evans)	1 hr Resp			5 M (pulmonary edema, enzyme changes associated with type 2 cell hyperplasia)	Boudreau et al. 1989 CdCl2	
9	Rat (Wistar)	3 hr Resp		0.4 M (mild hypercellularity at the bronchoalveolar junction and in adjacent alveoli)	4.6 M (persistent focal interstitial thickening, increased collagen, general hypercellularity)	Buckley and Bassett 1987b CdO dust	
		Bd Wt	0.4 M	4.6 M (15% decreased body weight)			
10	Rat (Sprague- Dawley)	1 hr Resp				Bus et al. 1978 CdCl2	
		Bd Wt		6.5 M (10.8% decreased body weight)			
11	Rat (Sprague- Dawley)	2 hr Resp	0.45 M		4.5 M (moderate to severe pneumonitis, hemorrhage, edema)	Grose et al. 1987 CdCl2	
		Bd Wt			4.5 M (20% decreased body weight)		

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
12	Rat (Sprague-Dawley)	Resp		0.45 M (significant increased absolute and relative lung weight)	4.5 M (severe pneumonitis, hyperplasia of type 2 cells and fibroblasts)	Grose et al. 1987 CdO dust	
13	Rat (Lewis)	Bd Wt	0.45 M			Hart 1986 CdO dust	
14	Rat (Wistar)	Bd Wt	0.17 M		1.6 M (interstitial pneumonitis)	Klimisch 1993 CdCl2	No histopathological examination.
15	Rat (Wistar)	Bd Wt	6.29 M			Klimisch 1993 CdS	No histopathological examination.
16	Rat (Fischer- 344)	Resp		0.88 F (degeneration of nasal olfactory epithelium)	8.8 (marked necrosis of alveolar ducts)	NTP 1995 CdO	
				^b 0.088 (alveolar histiocytic infiltrate and focal inflammation in alveolar septa)			
		Hepatic	2.6				
		Renal	2.6				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
17	Rat (Sprague-Dawley)	Resp			6 M (alveolar type 1 cell damage and necrosis)	Palmer et al. 1986 CdCl ₂	
		Endocr	6 M				
		Bd Wt	6 M				
18	Rat (Sprague-Dawley)	Gastro		132 (erosions of the stomach)		Rusch et al. 1986 CdCO ₃	
19	Rat (Sprague-Dawley)	Resp			6.1 M (emphysema)	Snider et al. 1973 CdCl ₂	
20	Rat (Sprague-Dawley)	Resp			61 M (pulmonary hemorrhage)	Snider et al. 1973 CdCl ₂	
21	Mouse (B6C3F-1)	Resp		0.88 (fibrosis and inflammation around the alveolar ducts, necrosis of the alveolar duct epithelium)		NTP 1995 CdO	
				0.088 (histiocytic infiltrates)			
		Hepatic	2.6				
		Renal	2.6				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
22	Hamster (Golden Syrian)	Resp		1.1 (moderate increase in PMN, 2-fold increase in acid phosphatase)	10.1 (severe pneumonitis)	Henderson et al. 1979 CdCl ₂	
23	Rabbit (New Zealand)	Resp		4.5 M (mild, multifocal interstitial pneumonitis)		Grose et al. 1987 CdCl ₂	
24	Rabbit (New Zealand)	Resp		0.45 M (increase in alveolar macrophages)	4.5 M (multifocal interstitial pneumonitis)	Grose et al. 1987 CdO dust	
Immunol/ Lymphoret							
25	Mouse (Swiss)	Bd Wt	0.11 F	0.45 M (unspecified decrease in body weight)		Graham et al. 1978 CdCl ₂	
26	Mouse (C57Bl/6)			0.88 F (reduction in spleen lymphocyte viability [35%], numbers, and humoral response (75%))		Krzyszyniak et al. 1987 CdCl ₂	
INTERMEDIATE EXPOSURE							
Death							
27	Rat (Wistar)				1 F (13/13 died by week 20)	Baranski and Sitarek 1987 CdO dusts	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
28	Rat (Fischer 344) 62 d 5 d/wk 6 hr/d				2.13 M (100% mortality by day 45)	Kutzman et al. 1986 CdCl ₂	
29	Rat (Wistar) 6 mo 40 hr/wk				0.09 (> 75% mortality by 11-12 months postexposure)	Oldiges et al. 1989 CdCl ₂	
30	Rat (Wistar) 6 mo 40 hr/wk				0.27 (> 75% mortality by 21-23 months postexposure)	Oldiges et al. 1989 CdS	
31	Rat (Wistar) 63d 24 hr/d				0.105 F (5/12 died)	Prigge 1978a CdO dust	
Systemic							
32	Rat (Wistar) 20 wk 5 d/wk 5 hr/d	Bd Wt	0.16 F		1 F (30-50% decreased body weight gain)	Baranski and Sitarek 1987 CdO dusts	
33	Rat (Wistar) 30 d 7 d/wk 22 hr/d	Resp		0.105 M (increased total bronchoalveolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdCl ₂	No histopathology examination.
		Hemato		0.105 M (45% increase in WBC)			

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
34	Rat (Wistar)	Resp	0.098 M	(increased total bronchoalveolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdO dust	No histopathology examination.
35	Rat (Wistar)	Resp	1.034 M	(increased total bronchoalveolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdS	No histopathological examination.
36	Rat (Fischer 344)	Resp	1.06 M	(marked fibrosis with significant increase in collagen)		Kutzman et al. 1986 CdCl ₂	
		Bd Wt	0.33	(14% decreased body weight)	2.13	(42-51% decreased body weight)	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
37	Rat (Fischer- 344)	6.33 hr/d 5 d/wk 13 wk	Resp	0.022 F	(epithelial degeneration in the larynx)	0.88	NTP 1995 CdO	(marked inflammation and moderate fibrosis in interstitium around alveolar ducts and terminal bronchioles)
			Cardio	0.88				
38	Rat (Fischer 344)	4 wks 5 d/wk 6 hr/d	Resp	0.1 M			Oberdorster et al. 1994 CdCl ₂	
			Cardio	0.88				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
39 Rat (Wistar)	63 or 90 d 24 hr/d	Resp		0.025 F (proliferations, histiocytic cell granulomas)		Prigge 1978a CdO dust	
		Hemato		0.052 F (increased hemoglobin and hematocrit)			
		Hepatic	0.105 F				
		Renal	0.105 F				
		Bd Wt		0.105 F (11% decrease in body weight)			
		Metab		0.105 F (decreased blood pH and pO ₂ , increased pCO ₂)			
40 Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (77% increased lung relative weight)		Prigge 1978b CdCl ₂	
		Hemato		0.204 F (8% increased hemoglobin, 5% increased hematocrit)			
		Hepatic	0.581 F				
		Renal	0.581 F				
		Bd Wt	0.394 F				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
41	Rat (Wistar)	Resp		0.204 F (70% increased lung relative weight)		Prigge 1978b CdCl ₂	
		Hemato		0.581 F (increased hemoglobin [12%], hematocrit [12%], total bilirubin [2-fold])			
		Hepatic	0.581 F				
		Renal	0.581 F				
42	Mouse (B6C3F1)	Bd Wt		0.394 F (12% decreased maternal weight gain)			
		Resp		0.088 M (Degeneration of nasal olfactory epithelium)		NTP 1995 CdO	
				0.022 (alveolar histiocytic infiltrates and squamous metaplasia of the larynx)			
		Cardio	0.88				
		Gastro	0.88				
		Hepatic	0.88				
		Renal	0.88				
		Bd Wt	0.88				

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
43	Mouse (BALB/c)	4 wks 5 d/wk 6 hr/d	Resp		0.1 M (increased neutrophils, LDH and beta-glucuronidase; pulmonary inflammation)		Oberdorster et al. 1994 CdCl ₂	
44	Rabbit (NS)	9 mo 21 d/mo 3 hr/d	Resp			4 (chronic pneumonia, emphysema)	Friberg 1950 Cd metal dust	
			Hemato		4 (eosinophilia, lower hemoglobin)			
			Renal			4 (proteinuria)		
45	Rabbit (NS)	7 mo 23 d/mo 3 hr/d	Resp			5.6 (emphysema)	Friberg 1950 Cd metal dust	
			Renal			5.6 (proteinuria in 6/10 surviving to the end of exposure)		
46	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp			0.4 M (lung interstitial inflammation, type 2 cell hyperplasia)	Johansson et al. 1984 CdCl ₂	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m³)	Less Serious (mg/m³)	Serious (mg/m³)		
Reproductive							
47	Rat (Wistar) 5 hr/d 5 d/wk 5 mo premating, mating, Gd 1-20		0.16 F			Baranski 1984 CdO	
48	Rat (Wistar) 20 wk 5 d/wk 5 hr/d			1 F (increased duration of estrous cycle)		Baranski and Sitarek 1987 CdO dusts	
49	Rat (Fischer 344) 62 d 5 d/wk 6 hr/d		1.06 M (t			Kutzman et al. 1986 CdCl2	
50	Rat (Fischer- 344) 6.33 hr/d 5 d/wk 13 wk		0.22 M 0.22 F	0.88 M (decreased spermatid counts 0.88 F (increased estrous cycle length)		NTP 1995 CdO	
Developmental							
51	Rat (Wistar) 5 hr/d 5 d/wk 5 mo premating, mating, Gd 1-20			0.02 F (altered performance on neurobehavioral tests)		Baranski 1984 CdO	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
52	Rat (Wistar) 4-5 mo 5 d/wk 5 hr/d			0.02 (altered performance on neurobehavioral tests)	0.16 (decreased pup viability)	Baranski 1985 CdO dusts	
53	Rat (Sprague-Dawley) 6.27 hr/d 7 d/wk Gd 4-19		0.4 F	1.7 F (decreased fetal body weight and reduced ossification)		NTP 1995 CdO	
54	Rat (Wistar) 21 d Gd 1-21 24 hr/d			0.581 (9% decreased fetal body weight, 12% increase in fetal alkaline phosphatase)		Prigge 1978b CdCl ₂	
55	Mouse (Swiss) 6.27 hr/d 7 d/wk Gd 4-17		0.04 F	0.4 F (decreased fetal body weight)		NTP 1995 CdO	
Cancer							
56	Rat (Wistar) 6 mo 40 hr/wk				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdCl ₂	
CHRONIC EXPOSURE							
Death							
57	Human 1-34 yr 5 d/wk 8 hr/d (occup)				6.8 M (2 fatalities from 14 years or 25 years of exposure to Cd dust)	Friberg 1950 Cd dust	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
58	Rat (Wistar) 413-455 d 7 d/wk 22 hr/d				0.095 M (6/20 died)	Oldiges and Glaser 1986 CdSO ₄	
59	Rat (Wistar) 18 mo 7 d/wk 22 hr/d				0.03 M (>75% mortality by 12 months postexposure)	Oldiges et al. 1989 CdCl ₂	
60	Rat (Wistar) 18 mo 7 d/wk 22 hr/d				0.09 (more than 25% died after 7 months [M] and 11 months [F] of exposure)	Oldiges et al. 1989 CdO dust	
61	Rat (Wistar) 18 mo 7 d/wk 22 hr/d				0.09 (>75% mortality after 12 months postexposure)	Oldiges et al. 1989 CdS	
62	Rat (Wistar) 18 mo 7 d/wk 22 hr/d				0.09 M (>25% mortality by 14 months of exposure)	Oldiges et al. 1989 CdSO ₄	
					0.09 F (>75% by 11 months postexposure)		
Systemic 63	Human	Renal	0.0001 ^C F			Buchet et al. 1990; Jarup et al. 2000; Suwazono et al. 2006 form not specified	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
64	Human 4-24 yr 5 d/wk 8 hr/d (occup)	Resp	0.025			Edling et al. 1986 CdO fume	
65	Human 30 yr 5 d/wk 8 hr/d (occup)	Renal	0.033		0.067 (pronounced proteinuria)	Elinder et al. 1985b CdO fume	
66	Human 30 yr 5 d/wk 8 hr/d (occup)	Renal	0.0153 M		0.0379 M (100% incidence of proteinuria in the cohort exposed to this level for 21 years)	Falck et al. 1983 CdO fume	
67	Human 30 yr 5 d/wk 8 hr/d (occup)	Renal	0.017		0.023 (9.2% incidence of proteinuria)	Jarup et al. 1988 CdO dust	
68	Human 30 yr 5 d/wk 8 hr/d (occup)	Renal	0.0367 M			Mason et al. 1988 form not specified	
69	Human 30 yr 5 d/wk 8 hr/d (occup)	Renal	0.027			Thun et al. 1989 CdO dust or fume	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
70	Rat (Wistar)	18 mo 7 d/wk 23 hr/d			0.0134 M (adenomatous hyperplasia in the bronchioalveolar area)	Takenaka et al. 1983 CdCl ₂	
Cancer							
71	Human	6 mo - 43 yr 7 d/wk 8 hr/d (occup)	Bd Wt 0.0508 M		0.1 M (CEL: 50-111 lung cancer deaths per 1000 workers; 45 year exposure)	Stayner et al. 1992 CdO dust or fumes	
72	Rat (Wistar)	18 mo 7 d/wk 22 hr/d			0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdCl ₂	
73	Rat (Wistar)	18 mo 7 d/wk 22 hr/d			0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdO dust	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference	Chemical Form	Comments
				NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)			
74	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas)	Oldiges et al. 1989	CdO fume	
75	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989	CdS	
76	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (CEL: lung bronchio-alveolar adenomas, adenocarcinomas, squamous cell carcinomas)	Oldiges et al. 1989	CdSO ₄	

Table 3-1 Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
77	Rat (Wistar) 18 mo 7 d/wk 23 hr/d				0.0134 M (CEL: lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas)	Takenaka et al. 1983 CdCl ₂	

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.00003 mg Cd/m³ (0.03 ug Cd/m³); concentration was adjusted for intermittent exposure (6.2 hours/day, 5 days/week) and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

c The chronic-duration inhalation MRL of 0.00001 mg Cd/m³ (0.01 ug Cd/m³) was calculated from the 95% lower confidence limit of the urinary cadmium level associated with a 10% increased risk of low molecular weight proteinuria (0.5 ug/g creatinine) estimated from a meta-analysis of select environmental exposure studies. An air concentration (together with an assumed dietary intake of 0.3 ug Cd/kg/day) which would result in this urinary cadmium concentration was estimated using the ICRP human respiratory tract model and a modification of the Nordberg-Kjellstrom pharmacokinetic model (see Appendix A for details on the meta-analysis and extrapolation to air concentration). This air concentration of 0.1 ug Cd/m³ was divided by an uncertainty factor of 3 for human variability and a modifying factor of 3.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolic; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; PMN = polymorphonuclear leukocyte; Resp = respiratory; WBC = white blood cells; wk = week(s); yr = year(s)

Acute (≤ 14 days)

Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation (Continued)

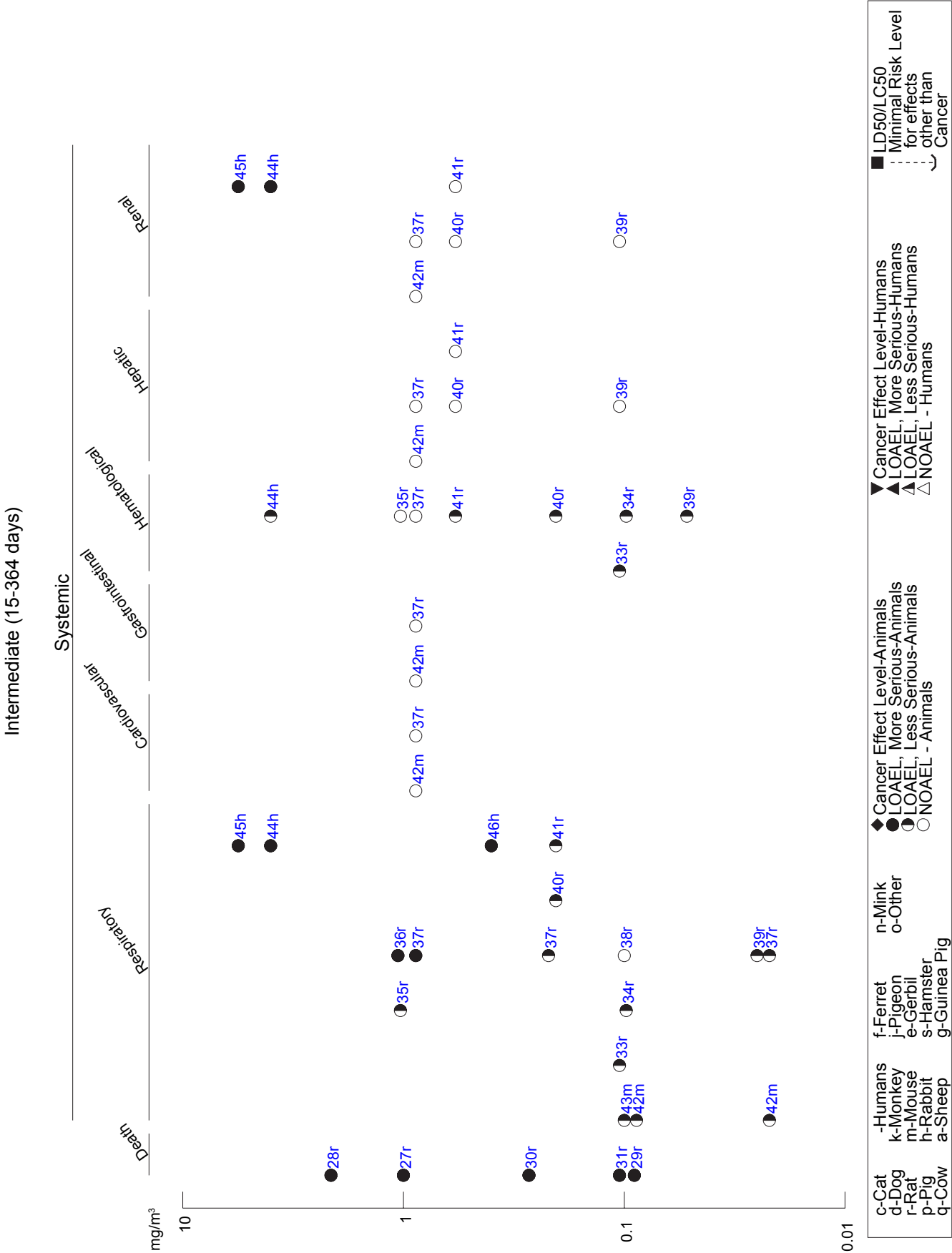


Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation (Continued)

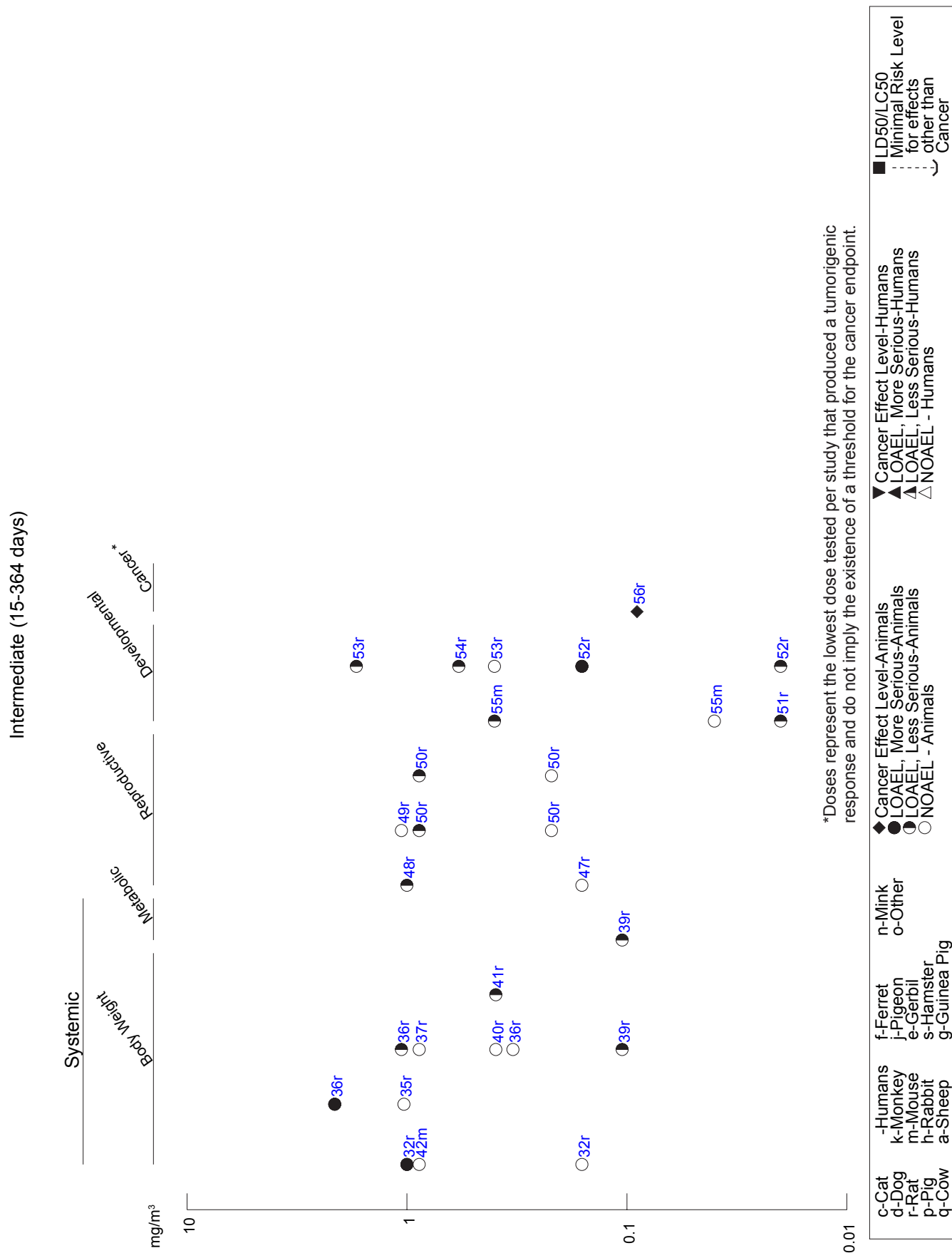
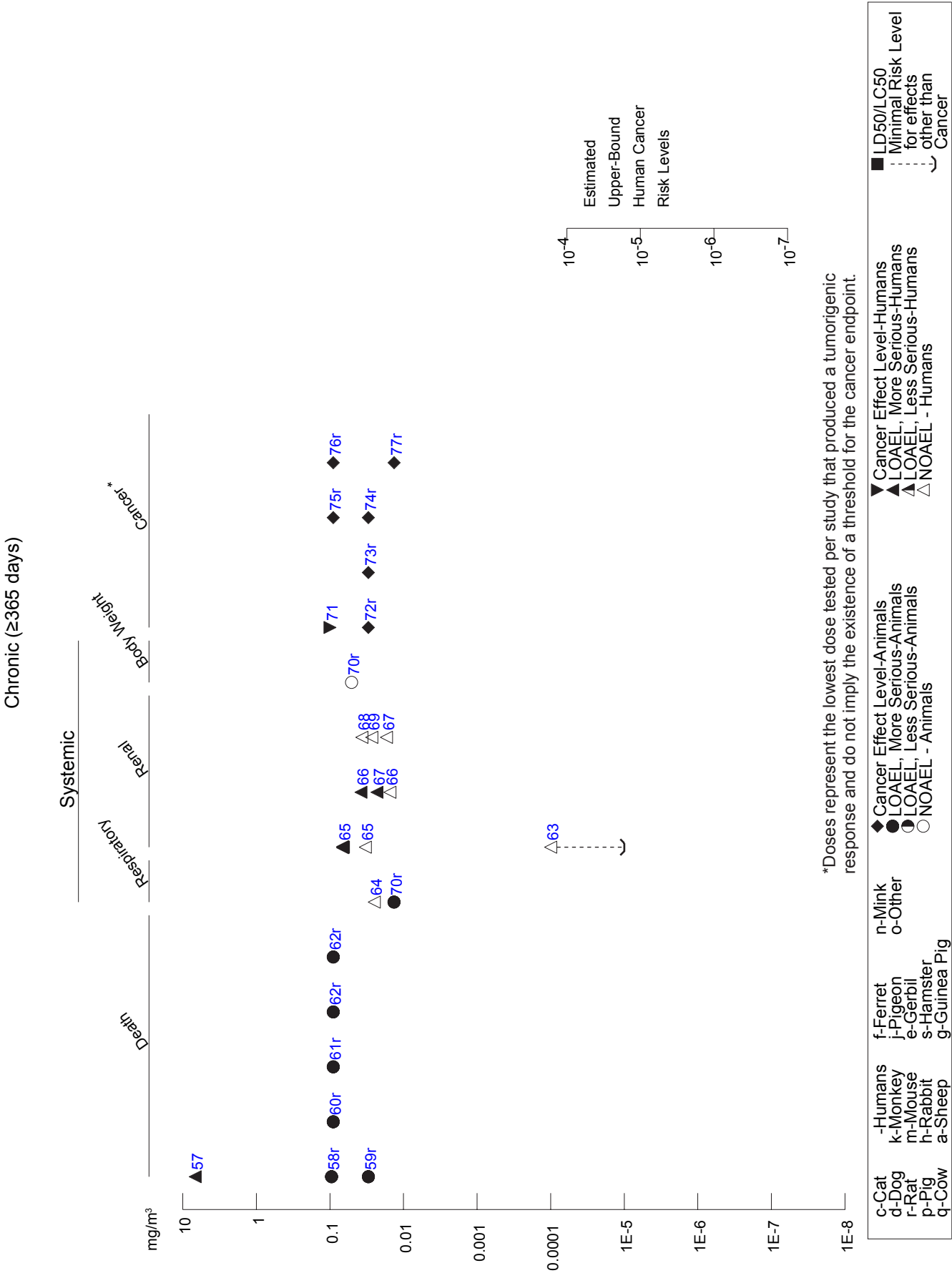


Figure 3-1 Levels of Significant Exposure to Cadmium - Inhalation (Continued)



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had no improvement in respiratory function. Precise estimates of cadmium concentrations leading to acute respiratory effects in humans are not currently available.

The initial symptoms of respiratory distress observed in the higher acute exposures do not occur following lower-level, longer-term inhalation exposures (Friberg 1950). Longer-term occupational exposure to levels of cadmium below those causing lung inflammation, however, have been reported to cause emphysema and dyspnea in humans (Bonnell 1955; Friberg 1950; Lane and Campbell 1954; Smith et al. 1960). Kjellström et al. (1979) reported a significant increase in deaths due to respiratory diseases in cadmium-exposed battery factory workers exposed for >5 years.

A significant, dose-dependent excess in the ratio of observed to expected deaths from bronchitis (i.e., standardized mortality ratio [SMR]=434) but not emphysema was found among 6,995 men occupationally exposed to cadmium for an average of 11 years (Armstrong and Kazantzis 1983). The dose level was not determined.

The earlier occupational studies did not control for the health effects of cigarette smoking. There is some evidence that cadmium may accelerate the development of emphysema in smokers. Leduc et al. (1993) report a case history of a 59-year-old male worker who smoked a pack of cigarettes per day since age 16, but had no prior history of respiratory disease in 1975 until developing emphysema in 1979 after inhaling various concentrations of cadmium (range of 0.0164–1.192 mg/m³, mean of 0.446 mg/m³, about nine times the threshold value of 0.050 mg/m³) for 4 years as a furnace operator. Very high levels of cadmium in air samples at the workplace and in the patient's blood, urine, and lung tissue confirmed massive exposures. Lung-function tests declined rapidly, with a faster than usual onset of emphysema compared to other smokers. The mean concentration of cadmium in a removed section of lung was 580 µg/g dry tissue, compared to 14 µg/g in three unexposed controls matched for age, sex, and smoking habit who had also undergone resection of a bronchial carcinoma. The authors state that this case supports the hypothesis for an etiological role of cadmium fume inhalation in the development of emphysema.

More recent studies that controlled for smoking report lung impairment in cadmium-exposed workers (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976). Cortona et al. (1992) measured respiratory function parameters in 69 smoking and nonsmoking male subjects (average age 45) who were exposed to concentrations of 0.008–1.53 mg/m³ of cadmium fumes over a period of several years in a factory that produced cadmium alloys (silver-cadmium-copper). Forced Expiratory Volume (FEV), Forced Vital Capacity (FVC), Residual Volume (RV), Transfer Factor by the carbon

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monoxide method (TLCO), and Transfer Coefficient (KCO) were measured in these exposed individuals. The study found that there were no significant differences in the FVC, FEV, TLCO, and KCO between the workers exposed to cadmium fumes and control (non-exposed) individuals. There was a significant increase in RV of >8% in exposed workers; this effect was notably greater in those with higher cumulative exposures to cadmium (>10%). It is uncertain how much of a factor on the increased RV was due to the tendency of smokers to develop an initial emphysematous alteration in lung tissue due to smoking.

Davison et al. (1988) evaluated lung function in 101 men who had manufactured copper-cadmium alloy in a plant in England for ≥ 1 years since 1926. The exposed men were compared to controls from the factory's other seven divisions matched for age and employment status. Smoking in exposed and control men was similar. Between 1951 and 1983, 933 measurements of airborne cadmium had been made, 697 with static samplers and 236 with personal samplers. The various sampling methods used before 1964 are no longer considered to be reliable, so estimates of air concentrations were made based on changes in production techniques, ventilation, levels of production, and discussions with occupational health physicians, industrial hygienist, the management, and the workers. Cadmium concentrations in air from 1926 to 1972 were determined to have declined from 0.6 to 0.156 mg/m³. In 1973, concentrations were 0.085 mg/m³; from 1974 to 1983, concentrations ranged from 0.034 to 0.058 mg/m³. The lung function of 77 of the men occupationally exposed to cadmium was significantly impaired compared to the unexposed controls, with the greatest abnormalities in the highest-dose group. Forced expiratory volume in one second, ratio of forced expiratory volume to forced vital capacity, transfer factor, or transfer coefficient were significantly lower than expected and radiographic total lung capacity, residual volume, and the ratio of these two were significantly higher than expected. The greatest abnormalities were observed in workers with the highest cumulative exposure and the highest liver cadmium levels. Regression of the lung transfer coefficient versus cadmium exposure indicated a linear relationship with no apparent threshold.

Smith et al. (1976) studied the pulmonary function of 17 high-exposure workers, 12 low-exposure workers, and 17 controls. Cadmium air concentrations where high-exposure subjects worked were >0.2 mg/m³. High-exposure subjects had worked at the plant a median of 26.4 years, with a maximum of 40.2 years, and low-exposure subjects had worked a median of 27.1 years, with a maximum of 34.8 years. Workers with high exposure to cadmium had significantly decreased the FVC compared to low-exposure workers and controls. Chest X-rays indicated mild or moderate interstitial fibrosis in 29% of high exposure workers. A dose-response relationship was found between FVC and urinary cadmium, and

with months of exposure to cadmium fume, but not cadmium sulfate aerosol. In an analysis of the smoking habits, there was no significant difference between the two cadmium-exposed groups with respect to the proportion of present or past cigarette smokers, the intensity or duration of cigarette smoking, or cigar or pipe smoking habits. The control subjects, however, had a significantly ($p < 0.05$) “higher” exposure to cigarette smoke than the cadmium exposed workers with substantially greater numbers of pack-years, cigarettes smoked per day, and years smoked. A step-down and multiple regression analyses with a dependent variable of FVC (as percent of predicted), and the independent variables, age-height, cigarette pack-years, and urinary cadmium, resulted in no indication that an interaction between the independent variables led to the observed relationship between FVC and cadmium excretion.

Other studies, however, have not shown a cadmium-related increase in impaired respiratory function. Edling et al. (1986) studied Swedish workers occupationally exposed to cadmium oxide fume from cadmium-containing solders. Cadmium-containing solder had been used at the plant from 1955 to 1978. The results from the lung-function analysis showed no significant difference in symptoms or lung function between the cadmium-exposed and the reference group. The exposed and the reference groups were similar with respect to sex, age, and height. There was a higher percentage of smokers in the reference group (52%) than in the exposed group (42%), but the difference was not statistically significant. The authors could not explain why significant differences in effects were not seen in these workers since other studies have shown significant effects at comparable cadmium exposure levels. The authors suggest that a possible bias could have been introduced if people who had worked for >5 years in the plant had changed their occupation because of lung disease, so that only “healthy” workers remained. Significant effects may also have been found if the reference group included workers other than those who worked with solder, but the purpose of the study was to resolve the effects of cadmium exposure among workers with similar occupations. Evaluating the data from smokers and nonsmokers separately also showed no significant impairment in lung function between smoking exposed and smoking unexposed or nonsmoking exposed and nonsmoking unexposed. The lung impairment due to smoking was observed in that smokers in both the exposed and unexposed groups had a somewhat deteriorated closing volume and other lung function indicators in accordance with previous studies on the effects of smoking. These results support the hypothesis that the response to occupational dust exposure differs from the response to tobacco smoking.

Another possible reason for differing results is that lung injury caused by high-level cadmium exposure may be partially reversible (Bonnell 1955; Chan et al. 1988), with a return towards normal several years

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after exposures have been significantly reduced. Chan et al. (1988) studied a cohort of 36 female and 8 male workers at a Singapore cadmium battery factory exposed to cadmium oxide dust. Cadmium concentrations in air were 0.03–0.09 mg/m³ (geometric means). Lung function was measured using spirometry, helium dilution, tidal sampling, X-ray, and respiratory symptoms. The recovery of lung function after reduction or cessation of occupational exposure to cadmium dusts was assessed. Total lung capacity increased following reduction of exposure and, following cessation of exposure, vital capacity, FEV, and prevalence of respiratory symptoms all improved. Blood and urine cadmium concentrations were considerably lower with the reduction or cessation of exposure and were consistent with a decrease in the cadmium air levels.

Additional respiratory symptoms less frequently reported in workers occupationally exposed to cadmium are chronic rhinitis and impairment or loss of the sense of smell (Adams et al. 1969; Bonnell 1955; Friberg 1950; Liu et al. 1985; Rose et al. 1992). The cause of these effects may be chronic irritation or necrosis of the nasal membranes, as they are generally found only in individuals with high-level exposure. An increased prevalence of abnormal paranasal radiographic findings in cadmium-exposed workers compared to other published reports on non-exposed populations was reported by Shaham et al. (1993).

Studies in animals confirm that inhalation exposure to cadmium can lead to respiratory injury. Single acute exposures in rats to 5–10 mg Cd/m³ as cadmium oxide dust, cadmium oxide fume, or cadmium chloride for 1–5 hours resulted in moderate to severe, multifocal interstitial pneumonitis, diffuse alveolitis with hemorrhage, increased lung weight, inhibition of macrophages, focal interstitial thickening, edema, and necrosis of alveolar type 1 cells leading to type 2 cell hyperplasia and fibroblasts (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart et al. 1989a; NTP 1995; Palmer et al. 1986). Similar results (i.e., severe pneumonitis) were seen in hamsters exposed to cadmium chloride at 10 mg/m³ for 30 minutes (Henderson et al. 1979) and in rabbits exposed to cadmium oxide dusts at 4.5 mg/m³ for 2 hours (Grose et al. 1987). Exposures in rats to cadmium chloride at 6.1 mg Cd/m³ 1 hour/day for 5, 10, or 15 days resulted in emphysema; a 3-day exposure to 61 mg Cd/m³ for 1 hour/day resulted in pulmonary hemorrhage (Snider et al. 1973). Repeated exposure to 0.088 mg Cd/m³ as cadmium oxide for 2 weeks resulted in minimal to mild alveolar histiocytic (macrophage) infiltration in rats and mice, focal inflammation surrounding alveolar ducts and extending into the adjacent alveolar septa in rats, and hyperplasia in tracheobronchial lymph nodes in mice (NTP 1995). At higher concentrations, the severity of these lesions increased (the severity of the lung lesions was scored as moderate at ≥ 0.88 mg Cd/m³) and necrosis of the epithelial lining of the alveolar ducts was observed at ≥ 0.26 mg Cd/m³ in rats and 0.88 mg Cd/m³ in mice. The NTP (1995) study also found significant

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increases in the incidence of lesions in the nasal cavity; minimal-to-mild degeneration of the olfactory epithelium was observed in rats and mice exposed to 0.88 mg Cd/m³ and hyperplasia and inflammation of respiratory epithelium were observed in rats at 2.6 mg Cd/m³.

Persistent damage has been reported in an animal model following a single intratracheal exposure to 25, 100, or 400 µg cadmium chloride/kg body weight (Driscoll et al. 1992). Although most BALF biochemical (lactate dehydrogenase, total protein, and N-acetylglucosaminidase) and cellular (neutrophils and lymphocyte numbers) parameters returned to control levels 28 days after exposure, histopathological alterations including inflammation and fibrosis were still present 90 days post-exposure and the incidence and severity of the lesions were greater at 90 days compared to 28 days.

Intermediate-duration exposure to cadmium results in similar respiratory effects as seen in the acute exposures. Concentration-related increases in the severity and types of respiratory lesions have been observed. Because the intermediate-duration studies used different exposure protocols, intermittent exposure studies were duration-adjusted to continuous exposure (Table 3-2) to facilitate comparisons across these studies. The lowest adverse effect level for lung effects was 0.004 mg Cd/m³ for alveolar epithelial hyperplasia in mice (NTP 1995). At 0.008–0.07 mg Cd/m³, inflammation and minimal fibrosis were observed in rats, mice, and rabbits (Johansson et al. 1984; NTP 1995; Oberdörster et al. 1994) and marked inflammation and moderate fibrosis were observed in rats at 0.17 mg Cd/m³ (NTP 1995). At ≥0.34 mg Cd/m³, emphysema and chronic pneumonia were observed in rats and rabbits (Friberg 1950; Prigge 1978b). In addition to the widely reported effects in the lungs, NTP (1995) reported minimal lesions in the larynx of rats (epithelial degeneration) and mice (squamous metaplasia) exposed to 0.022 mg Cd/m³ and minimal lesions in the nasal cavity in rats (inflammation of respiratory epithelium) and mice (degeneration of olfactory epithelium) exposed to 0.088 mg Cd/m³. The toxicity of cadmium to the respiratory tract following intermediate-duration exposure is highlighted by the NTP (1995) rat and mouse studies. As summarized in Table 3-3, rats and mice were exposed to five concentrations (0.022, 0.044, 0.088, 0.22, and 0.88 mg Cd/m³ as cadmium oxide) 6.33 hours/day, 5 days/week for 13 weeks. The earliest effects observed were alveolar histiocytic infiltrates, alveolar epithelial hyperplasia, and tracheal epithelial hyperplasia or squamous metaplasia; these lesions were all graded as minimal. With increasing concentrations, the severity of most lesions increased as did the type of lesion.

There are fewer chronic-inhalation exposure studies that specifically reported systemic respiratory effects. Oldiges and Glaser (1986) report increased lung weights (amount unspecified) in rats from exposure to either cadmium sulfate at 0.092 mg Cd/m³ or cadmium sulfide at 0.254 mg Cd/m³ for 22 hours/day,

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Table 3-2. Comparison of Lung Effects Across Intermediate-Duration Inhalation Studies

Species	Exposure frequency/duration	Adverse effect level (mg Cd/m ³)	Duration-adjusted adverse effect level (mg Cd/m ³)	Effect	Reference
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.022	0.004	Alveolar hyperplasia	NTP 1995
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.044	0.008	Alveolar histiocytic infiltrates and hyperplasia	NTP 1995
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.044	0.008	Minimal fibrosis	NTP 1995
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.088	0.017	Moderate inflammation	NTP 1995
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.22	0.017	Minimal fibrosis	NTP 1995
Mouse	6 hours/day, 5 days/week, 4 weeks	0.1	0.02	Inflammation	Oberdörster et al. 1994
Rat	24 hours/day, 7 days/week, 90 days	0.025	0.025	Proliferations	Prigge 1978a
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.22	0.04	Inflammation	NTP 1995
Rat	6.33 hours/day, 5 days/week, 13 weeks	0.88	0.17	Marked inflammation and moderate fibrosis	NTP 1995
Mouse	6.33 hours/day, 5 days/week, 13 weeks	0.88	0.17	Moderate fibrosis	NTP 1995
Rat	6 hours/day, 5 days/week, 62 days	0.33	0.06	Fibrosis	Kutzman et al. 1986
Rabbit	6 hours/day, 5 days/week 4–6 weeks	0.4	0.07	Inflammation	Johansson et al. 1984
Rabbit	3 hours/day, 21 days/month, 9 months	4	0.34	Pneumonia/emphysema	Friberg 1950
Rabbit	3 hours/day, 23 days/month, 7 months	5.6	0.53	Emphysema	Friberg 1950
Rat	24 hours/day, 7 days/week				Prigge 1978b

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Table 3-3. Severity of Respiratory Effects in Rats and Mice Exposed to Cadmium Oxide for 13 Weeks^a

	Concentration (mg Cd/m ³)					
	0	0.022	0.044	0.088	0.22	0.88
Male rats						
Lung						
Alveolar histiocytic infiltrate	—	— ^b	1.0 ^c	2.0	3.0	3.0
Alveolar epithelial hyperplasia	—	—	1.0	1.0	2.0	2.1
Inflammation	—	—	—	—	2.6	4.0
Fibrosis	—	—	—	1.0	2.0	2.7
Mediastinal lymph node						
inflammation	—	—	—	1.3	3.2	3.3
Larynx						
Epithelial degeneration		1.0	1.0	1.0	1.0	1.0
Nose						
Olfactory epithelium degeneration	—	—	—		1.0	3.0
Olfactory epithelium respiratory metaplasia	—	—	—	—	—	1.3
Olfactory epithelium squamous metaplasia	—	—	—	—	—	1.9
Respiratory epithelium inflammation	—	—	—	—	1.0	2.6
Respiratory epithelium degeneration	—	—	—	—	—	1.5
Female rats						
Lung						
Alveolar histiocytic infiltrate	—	—	1.0	2.1	3.0	3.0
Alveolar epithelial hyperplasia	—	—	1.0	1.0	2.0	2.1
Inflammation	—	—	—		1.6	3.5
Fibrosis	—	—	—	1.0	2.0	2.1
Mediastinal lymph node						
inflammation	—	—	1.0	1.5	3.6	4.0
Larynx						
Epithelial degeneration	—	1.0	1.0	1.0	1.0	1.0
Nose						
Olfactory epithelium degeneration	—	—	—	—	1.0	2.8
Olfactory epithelium respiratory metaplasia	—	—	—	—	1.0	1.0
Olfactory epithelium squamous metaplasia	—	—	—	—	—	1.4
Respiratory epithelium inflammation	—	—	—	1.0	1.8	1.8

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Table 3-3. Severity of Respiratory Effects in Rats and Mice Exposed to Cadmium Oxide for 13 Weeks^a

		Concentration (mg Cd/m ³)					
		0	0.022	0.044	0.088	0.22	0.88
Male mice							
Lung							
Alveolar epithelial hyperplasia	—	1.0	1.0	1.8	1.7	2.0	
Inflammation	—	—	—	3.0	2.2	2.7	
Fibrosis	—	—	1.0	1.0	1.0	1.0	
Tracheobronchial lymph node hyperplasia	—	—	1.0	2.3	2.4	2.7	
Larynx							
Squamous metaplasia	—	1.0	1.0	1.0	1.0	1.1	
Nose							
Olfactory epithelium degeneration	—	—	—	1.0	1.7	2.0	
Olfactory epithelium respiratory metaplasia	—	—	—	—	1.0	1.5	
Olfactory epithelium squamous metaplasia	—	—	—	—		1.0	
Respiratory epithelium hyaline droplets	—	—	—	—	1.0	1.0	
Female mice							
Lung							
Alveolar histiocytic infiltrate	—	1.0	1.0	2.0	2.0	3.0	
Alveolar epithelial hyperplasia	—	—	—	1.4	2.0	2.0	
Inflammation	—	—	—	2.3	2.1	2.9	
Fibrosis	—	—	1.0	1.0	1.0	1.0	
Tracheobronchial lymph node hyperplasia	—	—	1.0	1.5	2.0	2.4	
Larynx							
Squamous metaplasia	—	1.0	1.0	1.0	1.0	1.0	
Nose							
Olfactory epithelium degeneration	—	—	—	1.0	1.0	2.0	
Olfactory epithelium respiratory metaplasia	—	—	—	—	—	1.0	
Respiratory epithelium hyaline droplets	—	—	—	—	1.0	1.0	

^aAnimals were exposed for 6.33 hours/day, 5 days/week.^bNo lesions present or not significantly different from control group.^cSeverity score: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Source: NTP 1995

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7 days/week for 413–455 days. Takenaka et al. (1983) observed adenomatous hyperplasia in the bronchoalveolar region in rats from exposure to cadmium chloride at 0.0134 mg Cd/m³ for 23 hours/day, 7 days/week for 18 months.

The available data suggest that there may be species differences in the respiratory toxicity of cadmium. In a comparison of the pulmonary response to exposure to 0.1 mg Cd/m³ as cadmium chloride 6 hours/day, 5 days/week for 4 weeks, Oberdörster et al. (1994) found that the inflammatory response in the lungs of mice was greater than that of rats exposed to the same cadmium concentration. However, the cadmium lung burden in mice was twice as high as the rat's lung burden. In the NTP (1995) study, adverse lung effects were observed at lower concentrations in mice compared to rats, but at the higher concentrations, the severity of the lung effects were greater in the rats. Although these data suggest species differences in the pulmonary toxicity of cadmium, more information is needed to evaluate if there are differences at given lung burdens.

Based on differences in the pharmacokinetic properties of various cadmium compounds, it is expected that differences in toxicity would be observed. As discussed in Oberdörster (1992), cadmium chloride and cadmium oxide elicited similar responses following a single intratracheal dose, whereas no response was observed for cadmium sulfide. However, Glaser et al. (1990) found similar responses following repeated exposures to various cadmium compounds.

Hart and colleagues (Hart 1986; Hart et al. 1989a, 2001) demonstrated that repeated low-concentration exposure to cadmium results in the development of adaptive survival response. In rats exposed to 1.6 mg Cd/m³ as cadmium acetate 3 hours/day, 5 days/week, thickening of the alveolar septa and mononuclear cell and polymorphonuclear leukocyte aggregates were observed after 2 weeks of exposure (Hart 1986). However, the inflammatory response was decreased after 3 weeks of exposure and no significant histopathological alteration were observed in rats exposed for 4, 5, or 6 weeks. After 5 weeks of cadmium exposure, a single high concentration (8.4 mg Cd/m³) resulted in less pulmonary damage compared to non-pretreated animals (Hart et al. 1989a). Multiple pulmonary resistance factors appear to contribute to this resistance/tolerance. These factors include increased levels of metallothionein, glutathione, and γ -glutamylcysteine synthetase (Hart et al. 2001). However, as suggested by Hart et al. (2001), cadmium-adapted alveolar epithelial cells have a reduced ability to repair DNA damage and apoptotic cell death is attenuated in these cells; thus, cadmium adapted animals may be more susceptible to tumor formation.

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Cardiovascular Effects. Inhalation exposure to cadmium does not appear to have significant effects on the cardiovascular system. Most studies of workers occupationally exposed to cadmium have not found cadmium-related cardiovascular toxicity. In some studies, the mortality from cardiovascular disease was lower in the cadmium-exposed population. Armstrong and Kazantzis (1983) reported that a cohort of 6,995 British men occupationally exposed to cadmium for an average duration of 11 years had a significantly lower mortality from vascular disease.

Fifty-three male workers exposed to cadmium and lead and 52 male controls were examined for correlations in urine levels and blood pressure. The average duration of exposure was 12.5 years. Correlations between blood pressure and urinary cadmium in exposed workers were not significant after controlling for age or age and heart rate. Exposure to lead was a significant confounding factor (de Kort et al. 1987).

Friberg (1950) investigated the health of workers in a manufacturing plant that made cadmium-containing electrodes used in the production of batteries. Fifty-eight workers (30–50 years of age) were divided into two groups based on number of years at the plant. Workers were clinically examined for subjective symptoms and corresponding morphological or functional changes of the respiratory, cardiovascular, and excretory systems. The cardiovascular exam was largely unremarkable. Only a slight rise in blood pressure in a few cases was observed in Group 1. Electrocardiograms (EKG) were not significantly different from a matched control group in Group 1. Group 2 had neither increased blood pressure nor altered EKGs.

Kazantzis et al. (1988) studied mortality in a cohort of 6,958 cadmium-exposed male workers with average occupational exposures of 12 years. This was a follow-up study to the work of Armstrong and Kazantzis (1983). There was a significant deficit in deaths from cerebrovascular disease among men occupationally exposed to cadmium. There was no significant excess risk from hypertensive or renal disease.

Smith et al. (1980) studied 16 male high-exposure production workers and 11 male low-exposure office and supervisory workers for renal function. Average duration of exposure was 25 years. High-exposure workers were exposed to cadmium oxide concentrations of 0.23–45.2 mg/m³ and cadmium sulfide concentrations of 0.04–1.27 mg/m³. No difference was found in hypertension between high- and low-exposure workers, adjusted for age and weight or cigarette smoking.

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Sorahan and Waterhouse (1983) examined mortality rates in a cohort of 3,025 nickel-cadmium battery workers (2,559 males and 466 females). Cadmium levels in air ranged from 0.05 to 2.8 mg/m³, primarily as cadmium oxide. Duration of exposure ranged from 1 to >6 years. No increase in mortality from diseases of the circulatory system (e.g., hypertension) was seen in cadmium-exposed workers.

Staessen and Lauwerys (1993), in a study known as the Cadmibel Study (a cross-sectional population study), evaluated 2,327 people from a random sample of the population of four Belgian districts chosen to provide a wide range of environmental exposure to cadmium. Participants completed a questionnaire regarding their medical history, current and past occupations, smoking habits, alcohol consumption, and intake of medications. Urine and blood samples were taken, and pulse rate, blood pressure, height, and weight were recorded. Exposure to cadmium was considered to be by both the oral and inhalation routes. Cadmium levels in blood and urine were significantly increased in the high-exposure areas compared to the low-exposure areas ($p < 0.001$). Blood pressure was not correlated with the urine or blood cadmium levels. The prevalence of hypertension or other cardiovascular diseases was similar in all four districts, and was not correlated with urine or blood cadmium levels. A follow-up investigation of 692 participants of this study also showed no correlation with urine or blood calcium levels and the prevalence of hypertension after 5 years (Staessen et al. 2000). These results do not support a hypothesis that cadmium increases blood pressure, prevalence of hypertension, or other cardiovascular diseases.

One study found a statistically significant increase in blood pressure in exposed workers compared to controls (Thun et al. 1989), but mortality in this cohort was lower than expected (Thun et al. 1985).

There are limited data on the cardiotoxicity of cadmium in animals. No significant alterations in systolic blood pressure or histological alterations in the heart were observed in rats exposed to cadmium oxide concentrations as high as 0.88 mg Cd/m³ for 13 weeks (NTP 1995).

Gastrointestinal Effects. In the cohort he studied, Friberg (1950) found no association between inhalation cadmium exposure in workers and symptoms of gastrointestinal toxicity. Symptoms that had been reported in case histories from the 1920s included pain or tenderness at the epigastrium associated with nausea and some constipation. No other human studies report any cadmium associated gastrointestinal toxicity from inhalation exposure.

In the only animal study located, Rusch et al. (1986) observed erosion of the stomach in rats from exposure to cadmium carbonate at 132 mg Cd/m³ for 2 hours. Postmortem evaluation was performed at

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1, 3, 7, and 30 days postexposure. After the inhalation exposure in a whole-body chamber, rats were vacuumed to remove any cadmium carbonate dust adhering to the ventral and dorsal fur. The 132 mg Cd/m³ dose is relatively high. Three of the 10 test animals died during the 2-hour exposure so the significance of the gastrointestinal effect in this study is unclear.

Hematological Effects. The evidence concerning hematological effects following inhalation exposure to cadmium is conflicting. Lowered hemoglobin concentrations and decreased packed cell volumes have been observed in some studies of workers occupationally exposed to cadmium (Bernard et al. 1979; Friberg 1950; Kagamimori et al. 1986), but not in others (Bonnell 1955; Chan et al. 1988; Davison et al. 1988). The changes that were found often were not statistically significant (Bernard et al. 1979; Friberg 1950), and examination of bone marrow of some workers with lowered hemoglobin revealed no detectable abnormalities (Friberg 1950).

Conflicting results on the hematologic effect of cadmium after inhalation exposure have also been obtained with animal studies. Rabbits exposed to cadmium oxide dust at 4 mg/m³ for 3 hours/day, 21 days/month for 9 months developed eosinophilia and a slightly lower hemoglobin (Friberg 1950). In contrast, rats exposed to cadmium oxide dust at 0.052 mg Cd/m³ for 24 hours/day for 90 days had increased hemoglobin and hematocrit that were attributed to decreased lung function (Prigge 1978a). Prigge (1978b) also reported increased hemoglobin and hematocrit in rats continuously exposed to cadmium chloride at 0.204 mg Cd/m³ and higher for 21 days. Other studies report no Cd-related hematological effects. A nearly continuous 30-day exposure in rats to cadmium sulfide at 1.034 mg Cd/m³ had no effect on red blood cell counts (Glaser et al. 1986). A nearly continuous 218-day exposure in rats to cadmium oxide dust or fume at 0.090 mg Cd/m³ had no effect on a routine hematological evaluation (specific tests not reported) (Oldiges and Glaser 1986). A partial explanation for these conflicting results may be that Cd-induced anemia primarily results from impaired absorption of iron from the diet following gastrointestinal exposure to cadmium (see Section 3.2.2.2), and the amount of gastrointestinal exposure following cadmium inhalation is variable depending on the form and dose.

Musculoskeletal Effects. Case studies indicate that calcium deficiency, osteoporosis, or osteomalacia can develop in some workers after long-term occupational exposure to high levels of cadmium (Adams et al. 1969; Blainey et al. 1980; Bonnell 1955; Kazantzis 1979; Scott et al. 1980). Effects on bone generally arise only after kidney damage has occurred and are likely to be secondary to resulting changes in calcium, phosphorus, and vitamin D metabolism (Blainey et al. 1980).

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No studies were located regarding musculoskeletal effects in animals after inhalation exposure to cadmium.

Hepatic Effects. Liver effects are not usually associated with inhalation exposure to cadmium. Friberg (1950) reported some nonspecific signs of liver disease in some workers from a group exposed to cadmium in the air for 20 years. Test results included increased serum gamma-globulin, and other indicators of abnormal serum globulins, including the flocculation test results of a positive Takata reaction and/or an elevated thymol values. These tests (the latter of which are not used today) were nonspecific indicators of cirrhosis or hepatitis. The significance of these test results with respect to cadmium exposure is questionable. Subsequent studies on workers exposed to cadmium in the air have not reported adverse liver effects (Adams et al. 1969; Bonnell 1955).

Liver effects have occasionally been found in animal studies. Cats examined within one day of inhalation exposure to an unspecified concentration of cadmium oxide fume had a variety of hepatic lesions, and liver changes from cell granulation at low doses to fatty infiltration at high doses (Prodan 1932). Increased serum alanine aminotransferase activity, indicative of liver damage, was seen in rats exposed for 30 days to 0.1 mg/m³ cadmium, but activity had returned to normal 2 months after exposure (Glaser et al. 1986). Kutzman et al. (1986) reported an increased liver relative weight in rats from a cadmium chloride exposure at 1.06 mg Cd/m³ for 6 hours/day, 5 days/week, for 62 days. Increased liver weight was not observed from a continuous cadmium chloride exposure at 0.029 mg Cd/m³ for 255 days, from a continuous cadmium oxide exposure at 0.090 mg Cd/m³ for 218 days, or from a continuous cadmium sulfate exposure at 0.095 mg Cd/m³ for 413 days (Oldiges and Glaser 1986). Similar negative results were reported by Prigge (1978a, 1978b) for a 21-day exposure to cadmium chloride at 0.581 mg Cd/m³, and for a 63-day exposure to cadmium oxide at 0.105 mg Cd/m³ (a dose that was very toxic to the lungs). A continuous high-dose exposure to cadmium sulfide at 2.247 mg Cd/m³ for 105 days did result in an unspecified increase in liver weight in surviving rats (Oldiges and Glaser 1986). Cadmium accumulates in the liver as well as the kidney, the main target organ for cadmium toxicity. The resistance of the liver to toxic effects from cadmium may be related to a higher capacity of the liver to produce metallothionein that would bind to cadmium and would lower the concentrations of free cadmium ions (see Section 3.4.3).

Renal Effects. There is very strong evidence that the kidney is one of the main target organ of cadmium toxicity following extended inhalation exposure. The sensitivity of the kidney to cadmium was recognized in an early investigation of workers exposed to cadmium oxide dust and cadmium fumes in a factory producing nickel-cadmium batteries (Friberg 1950). These workers suffered from a high

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incidence of abnormal renal function, indicated by proteinuria and a decrease in glomerular filtration rate. Many studies examining cadmium workers have reported various effects on the kidneys. Similar signs of renal damage have been observed in many other studies of workers occupationally exposed to cadmium (Adams et al. 1969; Bernard et al. 1979; Beton et al. 1966; Bonnell 1955; Bustueva et al. 1994; Chia et al. 1989; Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Iwata et al. 1993; Jakubowski et al. 1987; Järup and Elinder 1993; Järup et al. 1988; Kjellström et al. 1977a; Liu et al. 1985; Mason et al. 1988; Piscator 1966; Roels et al. 1981b; Rose et al. 1992; Smith et al. 1980; Thun et al. 1989). Most of these studies did not report cadmium exposure levels; rather, urinary cadmium, blood cadmium, or cumulative exposures were used as biomarkers of exposure. Thus, these studies are not presented in the LSE table (Table 3-1). Selected occupational exposure studies are summarized in Table 3-4.

One of the first signs of kidney effects is tubular dysfunction characterized by an increased urinary excretion of low-molecular-weight proteins such as β 2-microglobulin, human complex-forming glycoprotein (pHC) (also referred to as α 1-microglobulin), and retinol binding protein or increased urinary levels of intracellular enzymes such as N-acetyl- β -glucosaminidase (NAG) (European Chemicals Bureau 2007; Järup et al. 1998b). Numerous occupational exposure studies have reported increases in urinary levels of these biomarkers (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985b; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Kawada et al. 1989; Roels et al. 1993; Shaikh et al. 1987; Thun et al. 1989; Toffoletto et al. 1992; Verschoor et al. 1987). At higher exposure levels, increased urinary levels of high-molecular-weight proteins such as albumin have been reported (Bernard et al. 1979, 1990; Chen et al. 2006a, 2006b; Elinder et al. 1985b; Mason et al. 1988; Roels et al. 1989, 1993; Thun et al. 1989), but there is some debate as to whether this represents glomerular damage (Bernard et al. 1979; Roels et al. 1989) or severe tubular damage (Elinder et al. 1985a; Mason et al. 1988; Piscator 1984).

Chronic exposure to very high cadmium levels can result in glomerular damage resulting in decreases in glomerular filtration rate (GFR) (Friberg 1950; Järup et al. 1995b; Roels et al. 1991). Järup et al. (1995b) found a dose-response relationship between blood cadmium levels and GFR in cadmium workers. At blood cadmium levels of 5.6 to <8.4 $\mu\text{g/L}$, 33.3% of the workers had decreased GFR (defined as $<80\%$ of referents); whereas all subjects with blood cadmium levels of ≥ 8.4 $\mu\text{g/L}$ exhibited a decreased GFR.

Another study did not find alterations in GFR in workers with urinary cadmium levels of approximately 11 $\mu\text{g/g}$ creatinine; however, an exacerbation of the age-related decline in maximal GFR was observed

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Table 3-4. Summary of Occupational Exposure Studies Examining Renal Effects

Population	Effect	Adverse effect level	Reference
Zinc-cadmium smelter workers (n=87)	Age-related decline in maximal GFR was exacerbated in workers with cadmium-induced microproteinuria.	U-Cd: 11.1 µg/g creatinine	Roels et al. 1991
Workers using cadmium pigments in plastic production or using cadmium in welding (n=27)	Significant increase in urinary β2M and NAG levels.	U-Cd: 5 µg/g creatinine	Verschoor et al. 1987
Cadmium alloy workers (n=164)	Higher incidence of increased urinary β2M levels (>250 µg/L cut-off) when urinary cadmium levels exceeded 10 µg/g creatinine on one or more occasions, as compared to workers who never exceeded the 10 µg/g creatinine level.	U-Cd: 10 µg/g creatinine	Toffoletto et al. 1992
Cadmium smelter workers (n=53)	Significant increase in urinary protein and β2M levels.	U-Cd: 13.3 µg/g creatinine	Shaikh et al. 1987
Non-ferrous smelter workers (n=58)	Significant increase in urinary β2M, RBP protein, pHc, albumin, and transferrin levels.	U-Cd: >10 µg/g creatinine	Bernard et al. 1990
Workers exposed to cadmium pigment dust (n=58)	Significant correlation between urinary cadmium and NAG levels; significant correlation with β2M at one of the two time points.	U-Cd: 1.1–1.4 µg/g creatinine	Kawada et al. 1989
Zinc-cadmium smelter workers (n=50)	Significant association between urinary cadmium levels and urinary levels of NAG, albumin, and transferrin. At higher urinary cadmium levels (10 µg/g creatinine), there were significant associations with RBP and β2M.	U-Cd: 4 µg/g creatinine	Roels et al. 1993
Battery workers (n=561)	10% prevalence of abnormal β2M levels (220 µg/g creatinine cut-off).	U-Cd: 1.5 µg/g creatinine for ≥60 years of age U-Cd: 5 µg/g creatinine for <60 years of age	Järup and Elinder 1994
Alkaline battery factory workers (n=102)	10% prevalence of renal dysfunction (β2M >380 µg/g creatinine; RBP >130 µg/g creatinine).	U-Cd: 10–15 µg/g creatinine	Jakubowski et al. 1987
Workers at a factory using cadmium-containing solders (n=60)	25% prevalence of abnormal β2M levels (300 µg/g creatinine cut-off).	U-Cd: 2–5 µg/g creatinine	Elinder et al. 1985a

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Table 3-4. Summary of Occupational Exposure Studies Examining Renal Effects

Population	Effect	Adverse effect level	Reference
Workers at nickel-cadmium battery factory (n=92)	Significant increase in pHc and NAG levels (after adjustment for age, gender, and race).	U-Cd: 5–10 µg/g creatinine	Chia et al. 1992
Cadmium smelter workers (n=85)	Significant increases in levels β2M and NAG levels and increased prevalence of abnormal levels of these biomarkers.	U-Cd: 5–10 µg/g creatinine	Chen et al. 2006a, 2006b
Alkaline battery factory workers (n=141)	10% prevalence of renal dysfunction (β2M >300 µg/L; RBP >300 µg/L).	B-Cd: 300 µg-years/L (30 years of 10 µg/L)	Jakubowski et al. 1992
Battery workers (n=440)	Approximately 10% prevalence of abnormal β2M levels (35 µg/mmol creatinine cut-off).	B-Cd: 5.6 µg/L Cumulative exposure: 691 µg-years/m ³	Järup et al. 1988
Cadmium recovery plant workers (n=45)	Significant association between cumulative exposure and urinary β2M, RBP, phosphate, and calcium and serum creatinine levels.	Cumulative exposure: 300 mg/m ³	Thun et al. 1989
Workers exposed to cadmium fumes (n=33)	Increased urinary β2M and protein levels (mean 6,375 µg/g creatinine and 246 mg/g creatinine, respectively) in 7 workers (mean in remaining 23 workers 53 µg/g creatinine and 34 mg/g creatinine).	Cumulative exposure: 1,137 µg/m ³ /years	Falck et al. 1983

U-Cd = urinary cadmium, B-Cd = blood cadmium; GFR = glomerular filtration rate; pHc = human complex-forming glycoprotein (also referred to as α1-microglobulin); NAG = N-acetyl-β-glucosaminidase; β2M = β2-microglobulin; prt = protein; RBP = retinol binding protein

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(Roels et al. 1991). Other studies reported increases in serum creatinine levels, which are suggestive of impaired GFR (Roels et al. 1989; Thun et al. 1989).

Depressed tubular resorption of other solutes such as enzymes, amino acids, glucose, calcium, copper, and inorganic phosphate have been reported in workers with signs of tubular proteinuria (Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Mason et al. 1988). An increased frequency of kidney stone formation has also been reported in cadmium workers (Elinder et al. 1985a; Falck et al. 1983; Järup and Elinder 1993; Kazantzis 1979; Scott et al. 1978; Thun et al. 1989; Trevisan and Gardin 2005). This effect is likely to be secondary to disruption of calcium metabolism due to kidney damage. Järup and Elinder (1993) calculated an incidence rate ratio (IRR) (after adjustment for age and calendar time) of 3.0 (95% CI 1.3–6.8) for the occurrence of kidney stones among workers with a cumulative exposure of $\geq 5000 \mu\text{g}/\text{m}^3$ years; the IRR was not significantly elevated at lower cumulative exposure levels. Significant increases in kidney stone formation were observed in workers with increased urinary cadmium (median of 3.7 $\mu\text{g}/\text{g}$ creatinine), blood cadmium (median of 7 $\mu\text{g}/\text{L}$), and urinary β_2 -microglobulin (median of 155 $\mu\text{g}/\text{g}$ creatinine). The increased kidney stone formation may be secondary to the cadmium-induced kidney damage disruption of calcium metabolism.

Hellström et al. (2001) evaluated the association between occupational cadmium exposure and end stage renal disease among cadmium workers and residents living near a cadmium facility; renal replacement therapy was used as a surrogate for renal disease. The standardized rate ratios (SRRs) (95% CI) were 2.1 (0.6–5.3) and 2.5 (0.7–6.5) in male workers aged 20–79 or 40–79 years, respectively. Although the SRRs were not statistically significant, the ratios were significantly elevated in residents presumably exposed to lower cadmium levels (see Section 3.2.2.2 for more information on these results). Studies examining the cause of death among cadmium workers have not found significant increases in the standardized mortality ratios (SMRs) for nephritis or nephrosis (Armstrong and Kazantzis 1983; Järup et al. 1998a) or nonmalignant renal disease (Thun et al. 1985).

The data from studies of cadmium workers provide strong, clear evidence that the kidney is a sensitive target following chronic exposure, but the data do not clearly identify a threshold of toxicity. The earliest indication of an effect on the kidney is an increase in urinary levels of low molecular weight proteins particularly β_2 -microglobulin, retinol binding protein, and pHc. However, there is some question as to the adversity of these early indicators because increased excretion of low molecular weight proteins precede the clinical manifestations (Bernard et al. 1997; Järup et al. 1998b). As noted by Bernard et al. (1997), the assessment of the health significance of changes affecting a biomarker involves localizing the

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changes in the sequence of events that ultimately results in compromised renal function and appreciating the probability that these changes may lead to a deterioration of renal function. Their guidelines for interpreting β 2-microglobulin levels in cadmium workers are presented in [Table 3-5](#).

Another aspect of interpreting alterations in renal biomarkers and assessing risk is the issue of the reversibility of cadmium-induced tubular dysfunction and impaired glomerular filtration rate. In workers exposed to high levels of cadmium, cessation of exposure does not generally result in a reversibility of kidney damage. Increases in urinary levels of β 2-microglobulin, retinol binding protein, or total protein (Elinder et al. 1985b; Järup et al. 1993; Mason et al. 1999; Piscator 1984; Roels et al. 1989; Thun et al. 1989) or a decrease in glomerular filtration rate (Järup et al. 1993; Piscator 1984; Roels et al. 1989) have been observed in workers years after cadmium exposure cessation. However, in workers exposed to low levels of cadmium, cessation of exposure resulted in decreased or no change in urinary β 2-microglobulin levels (McDiarmid et al. 1997; van Sittert et al. 1993). In studies by Roels et al. (1997) and Trzcinka-Ochocka et al. (2002), former cadmium workers were divided into groups based on historical cadmium levels and urinary β 2-microglobulin or retinol binding protein levels. Both studies found that the reversibility of tubular dysfunction was dependent on the cadmium body burden and the severity of microproteinuria at the time cadmium exposure was reduced or ceased. In the Roels study, significant decreases in retinol binding protein levels and no change in β 2-microglobulin levels were observed in workers whose urinary cadmium levels never exceeded 10 μ g/g creatinine. Decreases in β 2-microglobulin and retinol binding protein levels were also observed in workers whose β 2-microglobulin levels were <300 μ g/g creatinine or between 300 and 1,500 μ g/g creatinine and urinary cadmium levels were >10 μ g/g creatinine, but were never >20 μ g/g creatinine. However, a progression of microproteinuria (increased urinary levels of β 2-microglobulin and retinol binding protein levels) was observed in workers who had initial β 2-microglobulin levels >1,500 μ g/g creatinine and urinary cadmium levels >20 μ g/g creatinine. In contrast, Trzcinka-Ochocka et al. (2002) found decreases in β 2-microglobulin and retinol binding protein levels in groups of workers with initial β 2-microglobulin and retinol binding protein levels of \leq 300, >300, \leq 1,500, or \geq 1,500 μ g/g creatinine; in all groups, the initial mean urinary cadmium levels were >20 μ g/g creatinine. However, the risk of increased excretion of retinol binding protein was higher in the groups of workers with initial retinol binding protein levels of >300 μ g/g creatinine. Logistic regression analysis demonstrated that the initial level of retinol binding protein was the most important determinant in reversibility of tubular proteinuria and that the influence of urinary cadmium level or length of time since exposure cessation was not statistically significant.

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Table 3-5. Guidelines for Interpreting β 2-microglobulin Levels

β 2-Microglobulin level	Significance
<300 μ g/g creatinine	Normal value.
300–1,000 μ g/g creatinine	Incipient cadmium tubulopathy (possibility of reversibility after removal from exposure). No change in GFR.
1,000–10,000 μ g/g creatinine	Irreversible tubular proteinuria which may lead to accelerated decline in the GFR with age. GFR normal or slightly altered.
>10,000 μ g/g creatinine	Overt cadmium nephropathy usually associated with decreased GFR.

GFR = glomerular filtration rate

Source: Bernard et al. 1997

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The available occupational exposure data suggest that tubular dysfunction generally develops only after cadmium reaches a threshold concentration in the renal cortex. However, a number of factors can influence urinary levels of β 2-microglobulin or retinol binding protein and direct relationship between urinary levels of these proteins and a kidney cadmium concentration has not been established. Based on the findings of early occupational exposure studies, a number of investigators estimated that the “critical concentration” of cadmium in the renal cortex associated with increased incidence of renal dysfunction in an occupational setting was about 200 $\mu\text{g/g}$ wet weight (Friberg et al. 1974; Kjellström et al. 1977a; Roels et al. 1983); this corresponds to a urinary cadmium levels of 5–10 $\mu\text{g/g}$ creatinine (European Chemicals Bureau 2007). Although 10 $\mu\text{g/g}$ creatinine was initially established as a threshold urinary cadmium concentration, there is sufficient evidence to suggest that adverse effects occur at lower urinary cadmium levels (Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985b; Järup and Elinder 1994; Kawada et al. 1989; Roels et al. 1993; Verschoor et al. 1987).

Indications of renal dysfunction associated with airborne cadmium exposure has also been observed in residents living near a lead/zinc smelter in the United Kingdom with high cadmium stack emissions (Thomas et al. 2009) and a zinc smelter in Norway (Bråtveit et al. 2011). In both studies, the subjects were exposed to airborne cadmium and elevated cadmium levels in the soil. The Thomas et al. (2009) study found a significant association between urinary cadmium levels and modeled atmospheric cadmium concentrations. The mean urinary cadmium concentrations were 0.22 and 0.34 nmol/mmol creatinine (approximately 0.22 and 0.34 $\mu\text{g/g}$ creatinine) in males and females, respectively, in the Thomas et al. (2009) study and 0.44 and 0.42 $\mu\text{g/g}$ creatinine in males and females, respectively, in the Bråtveit et al. (2011) study; Bråtveit et al. (2011) also measured urinary cadmium levels in the residents living in a nonpolluted area and found no significant differences in urinary cadmium levels between the two groups. Thomas et al. (2009) found significant correlations between urinary cadmium levels and urinary NAG levels in males and females and pHc in females. Additionally, the study found a significant dose-response relationship between urinary cadmium levels and NAG levels above the reference level of 1.25 IU/mmol creatinine. Bråtveit et al. (2011) also found a significant association between urinary pHc levels and urinary cadmium levels; however, there were no significant differences in pHc levels between residents living in the polluted areas and the control area.

Early animal studies confirmed that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after a 4-month inhalation exposure to cadmium metal dust at 4 mg/m^3 for 3 hours/day, 21 days/month; histologic lesions were found after an additional 3–4 months of exposure (Friberg 1950). Friberg (1950) noted that the degree of proteinuria was not especially pronounced. Most

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subsequent studies using inhalation exposure have not found proteinuria (Glaser et al. 1986; Kutzman et al. 1986; Prigge 1978a, 1978b), primarily because the levels of exposure and durations of follow up (e.g., 1–5 mg/m³ for intermediate exposures; 0.2–2 mg/m³ for chronic exposures) that produce serious respiratory effects have not been sufficient to produce a critical concentration of cadmium in the kidney.

Dermal Effects. Dermal toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported dermal effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined dermal toxicity in humans or animals following inhalation exposure to cadmium.

Ocular Effects. Ocular toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported ocular effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined ocular toxicity in humans following inhalation exposure to cadmium.

Rats exposed to a single 2-hour inhalation exposure to about 100 mg Cd/m³ as cadmium pigments had excessive lacrimation 4 hours after exposure (Rusch et al. 1986), but this was likely due to a direct irritation of the eyes rather than a systemic effect.

Body Weight Effects. No data were found regarding the effects of inhaled cadmium on human body weights.

In animals, cadmium has been shown to significantly reduce body weights. An acute exposure to cadmium oxide fumes at 112 mg Cd/m³ for 2 hours (Rusch et al. 1986) and cadmium oxide dust at 4.6 mg Cd/m³ for 3 hours (Buckley and Bassett 1987b) resulted in a significant reduction of body weight in male rats. Cadmium chloride at 6.5 mg Cd/m³ for 1 hour or 4.5 mg Cd/m³ for 2 hours produced significant reductions in male rat body weights (Bus et al. 1978; Grose et al. 1987). Cadmium carbonate at 132 mg Cd/m³ for 2 hours slowed rat body weight gains (Rusch et al. 1986). NOAELs for acute cadmium chloride exposure have been reported at 0.45 mg Cd/m³ for 2 hours (Grose et al. 1987); 0.17 mg Cd/m³ for 6 hours/day for 10 days (Klimisch 1993); and 6 mg Cd/m³ for 2 hours (Palmer et al. 1986). NOAELs for cadmium sulfide and cadmium selenium sulfide were much higher at 99 mg Cd/m³ for 2 hours and 97 mg Cd/m³ for 2 hours, respectively (Rusch et al. 1986). The effect of cadmium on body weight gain

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appears to compound-related, with cadmium chloride the most toxic and cadmium sulfide the least toxic. These compound-related differences are probably related to difference in absorption.

The body weight response also appears to be duration-related; lower NOAELs and LOAELs have been identified for intermediate-duration exposure. Levels of cadmium that significantly reduce rat body weights when administered for an intermediate exposure duration have been reported for cadmium chloride at around 1 mg Cd/m³ for female and male rats (Baranski and Sitarek 1987; Kutzman et al. 1986), for cadmium chloride at around 0.394 mg Cd/m³ for pregnant female rats (Prigge 1978a), and for cadmium dusts at 0.1 mg Cd/m³ for female rats (Prigge 1978a). NOAELs have been reported for intermediate exposures to cadmium chloride at 0.394 mg Cd/m³ for female nonpregnant rats (Prigge 1978a), 0.33 mg Cd/m³ for rats (Kutzman et al. 1986), and 0.0508 mg Cd/m³ for male rats (Takenaka et al. 1983). NOAELs have been reported for intermediate exposures to cadmium oxide dust at 0.16 mg Cd/m³ for female rats (Baranski and Sitarek 1987) and 0.45 mg Cd/m³ for male rabbits (Grose et al. 1987); and for cadmium sulfide at 1.034 mg Cd/m³ for male rats (Glaser et al. 1986). A NOAEL for chronic exposure in rats to cadmium sulfate has been reported as 0.95 mg Cd/m³ (Oldiges and Glaser 1986).

Other Systemic Effects. Yellow discoloration of the teeth has occasionally been reported in workers occupationally exposed to high levels of cadmium (Friberg 1950; Liu et al. 1985). No data were located to indicate that this was related to any functional impairment.

3.2.1.3 Immunological and Lymphoreticular Effects

There is limited evidence for immunological effects following inhalation exposure to cadmium. The blood of workers exposed to cadmium for 1–14 years had a slight but statistically significant decrease in the generation of reactive oxygen species by leukocytes compared to unexposed controls (Guillard and Lauwerys 1989). The toxicological significance of this effect is unclear.

Karakaya et al. (1994) measured blood and urine concentrations of cadmium, and serum IgG, IgM, and IgA in a group of 37 males employed in zinc/cadmium smelters and a small Cd-electroplating plant. Blood cadmium concentrations were significantly higher in exposed workers compared to controls in both the urine (2.39 versus 0.69 µg/100 mL, p<0.001) and the blood (5.55 versus 2.01 µg/g creatinine, p<0.05). No differences between the exposed and control serum concentrations of IgG, IgM, and IgA populations were observed. No changes in blood counts of white blood cells (lymphocyte, neutrophil, and eosinophil)

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were found between exposed and control populations, except for significantly increased monocyte counts. No other studies were located regarding immunological effects in humans following inhalation exposure to cadmium.

Acute inhalation exposure to cadmium chloride in mice at 0.190 mg Cd/m³ for 2 hours can affect immune function, causing suppression of the primary humoral immune response (Graham et al. 1978). The NOAEL for immunological effects from the study by Graham et al. (1978) was 0.11 mg Cd/m³. Krzystyniak et al. (1987) reported spleen lymphocyte cytotoxicity at 0.88 mg Cd/m³ for 1 hour.

At intermediate-duration exposures, Kutzman et al. (1986) observed increased spleen relative weights and lymphoid hyperplasia from inhalation of cadmium chloride aerosols at 1.06 mg Cd/m³ 6 hours/day, 5 days/week for 62 days. Prigge (1978b) also observed increased relative spleen weights in pregnant females at 0.394 mg Cd/m³ for an exposure of 24 hours/day for 21 days during gestation. Oldiges and Glaser (1986) observed enlarged thoracic lymph nodes in dead animals in a chronic-exposure study with cadmium sulfate at 0.092 mg Cd/m³ for 22 hours/day, 7 days/week for 413–455 days; and in an intermediate study with cadmium oxide dust at 0.090 mg Cd/m³ for 22 hours/day, 7 days/week for 218 days. However, other studies have found no effect on natural killer cell activity or viral induction of interferon in mice (Daniels et al. 1987). Evidence concerning the effect of inhalation exposure to cadmium on resistance to infection is conflicting, because the same exposure decreases resistance to bacterial infection while increasing resistance to viral infection (Bouley et al. 1982). The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#).

3.2.1.4 Neurological Effects

Neurotoxicity is not generally associated with inhalation exposure to cadmium, although a few studies have specifically looked for neurological effects. Hart et al. (1989b) reported that in a group of 31 men occupationally exposed to cadmium in a refrigerator coil manufacturing plant (average exposure=14.5 years) there was a modest correlation between cadmium exposure and decreased performance on neuropsychologic tests for attention, psychomotor speed, and memory. The limited number of men studied makes it difficult to evaluate the significance of this effect.

Rose et al. (1992) studied the presence and severity of olfactory impairment in workers chronically exposed to cadmium fumes generated during a brazing operation. Detailed occupational history, medical

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history, and smoking history, and symptoms were collected for 55 workers. Body burden was estimated using urinary cadmium levels, and renal damage was assessed by urinary β_2 -microglobulin levels. Olfactory test scores from these workers were compared to a reference group of 16 male subjects that were selected according to the following criteria: (1) no history of taste or smell complaints, (2) no history of surgery to the upper respiratory tract, (3) no upper respiratory tract infection within 2 days of testing, and (4) no history of having been tested. The dose of the cadmium oxide fume received by the workers being evaluated in this study was not reported or estimated. For both the exposed workers and the reference group, 38% were smokers. A significant olfactory impairment was observed in the workers compared to the reference group ($p < 0.003$). Thirteen percent of the workers were either moderately or severely hyposmic compared to none in the reference group, 44% of the workers were mildly hyposmic compared to 31% of the reference group, and only 44% of workers were normosmic. Although the odor-identification test findings for workers were similar to those of the reference group, butanol detection threshold scores were significantly lower in the worker population ($p < 0.005$). The workers with both higher urinary cadmium levels and tubular proteinuria had the most significant olfactory dysfunction, with a selective defect in odor threshold. The results suggest that chronic occupational cadmium exposure sufficient to cause renal damage is also associated with impairment in olfactory function. Some limitations of the study are that historical exposure to other confounders cannot be ruled out, the classification for nephrotoxicity is based on a single 24-hour urine β_2 -microglobulin level, and the smoking history of the reference group was unknown. No other human neurological studies from inhaled cadmium were found.

In rats, cadmium carbonate produced tremors from exposure to 132 mg Cd/m^3 for 2 hours, and cadmium fumes produced reduced activity at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986). Studies on continuous exposure to cadmium for 30 days have shown no neurological effects at 0.105 mg Cd/m^3 for cadmium chloride, 0.098 mg Cd/m^3 for cadmium dusts, or 1.034 mg Cd/m^3 for cadmium sulfide (Glaser et al. 1986). Cadmium chloride had no neurological effects at 0.33 mg Cd/m^3 for 5 days/week, 6 hours/day for a total of 62 daily exposures, but did significantly increase relative brain weight at 1.034 mg Cd/m^3 (Kutzman et al. 1986). No other studies were located regarding neurological effects in adult animals after inhalation exposure to cadmium. Neurological effects in offspring of rats exposed to cadmium by inhalation during gestation are discussed in Section 3.2.1.5. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

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3.2.1.5 Reproductive Effects

Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects.

Gennart et al. (1992) studied male reproductive effects of cadmium in 83 occupationally exposed blue-collar Belgian workers in two smelting operations. The workers were exposed to cadmium in dust and fumes. Information was recorded on age, residence, education, occupational and health history, actual and previous occupations, smoking habits, and coffee and alcohol consumption. Fertility parameters included dates of birth of wife and husband, date of marriage, and number of children born alive and their dates of birth. Blood and urine samples were also collected from each worker. Some cadmium workers had been excessively exposed; 25% of them already had signs of kidney dysfunction as evidenced by microproteinuria and/or a serum creatinine level >13 mg/L. No effects were observed on male fertility as evidenced by no significant influence of cadmium on the probability of a live birth. The limitation of this study, as described by the authors, included the fact that the wives were not interviewed and, therefore, factors that could have influenced their reproductive ability were not considered.

Men occupationally exposed to cadmium at levels causing renal damage had no change in testicular endocrine function, as measured by serum levels of testosterone, luteinizing hormone, and follicle-stimulating hormone (Mason 1990).

Noack-Fuller et al. (1993) measured concentrations of cadmium, lead, selenium, and zinc in whole semen and seminal fluid of 22 unexposed men (13 were smokers) to evaluate intra-individual variability and to examine the statistical association between element concentrations and semen characteristics and sperm motion parameters. None of the men had any known occupational exposure to cadmium.

Concentrations of cadmium were similar in semen and seminal plasma (0.40 ± 0.23 and 0.34 ± 0.19 $\mu\text{g/L}$, respectively). Sperm motility ($p < 0.02$), linear velocity ($p < 0.001$), and curvilinear velocity (CV) ($p < 0.002$) were significantly correlated with semen cadmium levels. Intra-individual coefficients of variation for sperm count ($\text{CV} = 46 \pm 4\%$) and sperm concentration ($\text{CV} = 37 \pm 6\%$) showed the highest variability. No positive correlation was found between cadmium concentration in semen and sperm density. The smokers had slightly elevated levels of cadmium. The concentrations of cadmium in semen of these volunteers were very low. Additional studies are needed (preferably with larger sample sizes) to evaluate the robustness of this association between cadmium (at the low levels detected) and sperm motion parameters. Saaranen et al. (1989) measured cadmium, selenium, and zinc in seminal fluid and

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serum in 64 men, half of whom were smokers. Smokers had significantly higher serum cadmium concentration than nonsmokers. Seminal fluid cadmium was also elevated in smokers, and was higher than serum cadmium in smokers consuming >20 cigarettes daily. Semen quality was measured for volume, sperm density, morphology, motility, and number of immature germ cells. No differences were found in semen quality or fertility between smokers and nonsmokers. There was no significant correlation between seminal fluid cadmium levels and semen quality or fertility.

Xu et al. (1993a) measured trace elements in blood and seminal plasma and their relationship to sperm quality in 221 Singapore men (age range 24–54; mean 34.8) who were undergoing initial screening for infertility. Men with significant past medical history and those who had been occupationally exposed were excluded. Parameters monitored included semen volume and sperm density, motility, morphology, and viability. Graphite furnace atomic absorption was used to determine cadmium concentration in blood and semen. No differences were observed in sperm quality (density, motility, morphology, volume, and viability) of the 221 men compared to a cohort of 38 fertility proven men (wives had recently conceived). Cadmium levels in blood did have a significant inverse relationship with sperm density ($r=-0.15$, $p<0.05$) in oligospermic men (sperm density <20 million/mL), but not in normospermic men. There was a significant reduction in sperm count in men with blood cadmium of $>1.5 \mu\text{g/L}$. Also, there was a weak negative correlation between defective sperm and concentration of cadmium in semen ($r=-0.21$, $p<0.05$). The volume of semen was inversely proportional to the cadmium concentration in semen ($r=-0.29$, $p<0.05$). These findings suggest that cadmium may have an effect on the male reproductive system. Limitations of the study include lack of control for potential confounding factors such as the lower levels of zinc in seminal plasma, and the validity of using infertile men as the study group (i.e., again because of confounding factors that may be affecting both cadmium levels and sperm levels).

A postmortem study of men occupationally exposed to cadmium who died from emphysema found high levels of cadmium in their testes, but no histologic lesions other than those attributable to terminal illness (Smith et al. 1960)

Russian women occupationally exposed to cadmium concentrations up to 35 mg/m^3 had no irregularities in their menstrual cycles (Tsvejkova 1970). Fertility and other indices of reproductive function were not measured. No studies were located that showed reproductive effects in women following inhalation exposure to cadmium.

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In rats, exposure to cadmium oxide dusts at 1 mg Cd/m³ for 5 hours/day, 5 days/week for 20 weeks, increased the duration of the estrous cycle (Baranski and Sitarek 1987). Male and female rats exposed to cadmium concentrations of 1.06 mg/m³ as cadmium chloride for 6 hours/day, 5 days/week for 62 days and subsequently mated with unexposed controls showed no loss in reproductive success measured by viable embryos and preimplantation losses, but males did have an increased relative testes weight (Kutzman et al. 1986). Similarly, no alterations in fertility in female rats exposed to 0.16 mg Cd/m³ as cadmium oxide for 5 months prior to mating with unexposed males and during the mating and gestation periods (Baranski 1984). Tsvetkova (1970) studied rats exposed to cadmium sulfate aerosols at 2.8 mg Cd/m³ before and during pregnancy. A lengthening of the estrous cycle was observed 2 months after the start of exposure in one-half of the exposed animals. By the fourth month, diestrus was 6.2 days in the exposed group compared to 1.2 days in controls. An increased in estrous cycle length was also observed in rats exposed to 0.88 mg Cd/m³ as cadmium oxide for 13 weeks (NTP 1995); this study also reported a significant decrease in spermatid counts in males exposed to the same cadmium concentration. No other studies were found on reproductive effects in animals. The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#).

3.2.1.6 Developmental Effects

Russian women occupationally exposed to cadmium at concentrations ranging from 0.02 to 35 mg/m³ had offspring with decreased birth weights compared to unexposed controls, but without congenital malformations (Tsvetkova 1970). No association was found between birth weights of offspring and length of maternal cadmium exposure. Moreover, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight (Tsvetkova 1970). A nonsignificant decrease in birth weight was found in offspring of women with some occupational exposure to cadmium in France; however, no adverse effects were documented in these newborns (Huel et al. 1984). Huel et al. (1984) used hair samples to estimate exposure, and this method is limited without controls to distinguish between exogenous and endogenous sources. No other studies were located regarding developmental effects in humans after inhalation exposure to cadmium.

In utero exposure to cadmium results in significant decreases in pup viability, fetal body weight, pup body weight gain, delays in ossification, and impaired performance on neurobehavioral tests. Decreases in pup viability (percentage of pups born alive that survived until postnatal day 4) were observed in the offspring of rats exposed to 0.16 mg Cd/m³ as cadmium oxide for 5 months prior to mating and during

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mating and gestation day 1–20 (Baranski 1984). Decreases in fetal body weight were observed in the offspring of rats exposed to ≥ 0.581 mg Cd/m³ as cadmium chloride (Prigge 1978b) or cadmium oxide (NTP 1995) and mice exposed ≥ 0.4 mg Cd/m³ as cadmium oxide (NTP 1995); maternal toxicity (decreased body weight gain and/or hypoactivity and dyspnea) were also observed at these exposure levels. Although Baranski (1984) did not find significant alterations in birth weight, a decrease in pup body weight gain was observed in the offspring of rats exposed to 0.16 mg Cd/m³ as cadmium oxide. Delays in skeletal ossification have also been observed in the offspring of rats and mice exposed to 1.7 mg Cd/m³ as cadmium oxide (NTP 1995); although Baranski (1985) also reported a delay in ossification in the offspring of rats, it is unclear whether the effect was observed at 0.02 mg Cd/m³, 0.16 mg Cd/m³, or both.

Baranski (1984, 1985) evaluated the potential of cadmium to induce neurobehavioral effects in the offspring of rats exposed to 0.02 or 0.16 mg Cd/m³ as cadmium oxide for 5 months prior to mating, during mating and gestation day 1–20; the studies reported similar effects and it is unclear whether the papers are reporting the results from separate experiments. The neurobehavioral alterations included decreased exploratory motor activity and avoidance acquisition in 3 month old male and female offspring, respectively, exposed to 0.02 mg Cd/m³. At 0.16 mg Cd/m³, decreased avoidance acquisition in 3 month old female offspring, exploratory motor activity in 3 month old male and female offspring, ambulations in open field test in 5 month old male offspring, and spontaneous mobility in male offspring and prolongation of latency in negative geotaxis test.

3.2.1.7 Cancer

The relationship between occupational exposure to cadmium and increased risk of cancer (particularly lung and prostate cancer) has been explored in a number of occupational exposure studies. The results of these studies are conflicting and the carcinogenicity of cadmium has not been unequivocally established. Overall, the results provide suggestive evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium. Initial studies indicated an elevation in prostate cancer among men occupationally exposed to cadmium (Kipling and Waterhouse 1967; Kjellström et al. 1979; Lemen et al. 1976), but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant (Elinder et al. 1985c; Kazantzis et al. 1988; Sorahan 1987; Sorahan and Esmen 2004; Thun et al. 1985). Based on an analysis of the mortality data from a 5-year update of the cohort from 17 plants in England and a review of the other epidemiological evidence, Kazantzis et al. (1992) concluded that cadmium does not appear to act as a prostatic carcinogen.

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Significant increases in mortality from lung cancer have been reported in workers employed at a U.S. cadmium recovery facility (Stayner et al. 1992a; Thun et al. 1985), nickel-cadmium battery facilities in England (Sorahan 1987) and Sweden (Järup et al. 1998a), and in a cohort of workers at cadmium processing facilities and/or smelters (Ades and Kazantzis 1988; Kazantzis et al. 1988). However, no clear relationships between level and duration of cadmium exposure and lung cancer risk have been established and many of these studies did not account for confounding exposure to other carcinogenic metals (particularly arsenic and nickel) and cigarette smoking.

The possible association between occupational exposure to cadmium and lung cancer was investigated in several studies of a cohort of workers employed at a U.S. cadmium recovery facility. The cohort was initially examined by Lemen et al. (1976) who found a significant increase in deaths from malignant neoplasms of the respiratory tract among hourly workers employed for at least 2 years between 1940 and 1969. A re-examination of the cohort (deaths through 1978) also found statistically significant standardized mortality rates (SMRs) for malignant neoplasms in the respiratory tract (Thun et al. 1985). To adjust for possible arsenic exposure (between 1918 and 1925, the facility functioned as an arsenic smelter), workers were divided based on year of hire. Mortality from lung cancer was significantly elevated in workers hired prior to 1926 and among workers hired after 1926 with 2 or more years of employment. Dividing the workers into three exposure groups based on estimated cumulative exposure resulted in a significant dose-related trend for lung cancer deaths; in the highest exposure group (cumulative exposures >8 years-mg/m³), a 2- to 8-fold increase in the risk of lung cancer deaths was observed (Thun et al. 1985). A subsequent analysis of these data (workers followed through 1985) used comparisons of rates with the cohort rather than the U.S. population (Stayner et al. 1992a). Lung cancer mortality was significantly increased among non-Hispanic whites, among workers with the highest cumulative exposure ($>2,291$ days-mg/m³), and among workers with the longest time since first exposure (>20 years). Lamm et al. (1992, 1994) used nearly the same data set for the U.S. cohort as Stayner et al. (1992a) in a nested case-control analysis that used the period of hire as a surrogate for arsenic exposure. Based on this analysis as a means to control for the confounding factor of arsenic exposure, Lamm et al. (1992, 1994) reported no residual association of lung cancer with cadmium. They also reported that cases were eight times more likely to have been cigarette smokers than were controls. Lamm et al. (1992, 1994) conclude that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk, not cadmium exposure.

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The reasons for these conflicting conclusions based on the same cohort data are unclear. Doll (1992) suggested some possible reasons including: (1) that the total number of cases was small ($n=25$) and that only 21 of these cases were included in both studies (i.e., each study included some cases that were not included in the other study); (2) that Stayner et al. (1992a) used national rather than regional mortality rates; (3) that the Lamm et al. (1992, 1994) control series was overmatched, although the matching by date of hire was necessary to control for arsenic exposure; and (4) that there are some concerns about the validity (i.e., biological relevance) of the dose-response-models used by Stayner et al. (1992a). In a response to Doll (1992), Stayner et al. (1993) reported that use of regional mortality rates would increase rather than decrease support for their conclusion, and that the nested case-control analysis of Lamm et al. (1992) used overmatched controls. Stayner et al. (1993) provided additional analyses including the use of the Armitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure. Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from time sheet records, to better resolve the potential confounding affects of arsenic. Poisson regression was used to investigate risks of mortality from lung cancer in relation to four concentrations of accumulative exposure to cadmium (<400 , $400-999$, $1,000-1,999$, and $>2,000$ mg-days/ m^3). After adjustment for age attained, year of hire, and Hispanic ethnicity; Sorahan and Lancashire (1997) report a significant positive trend ($p<0.05$) between cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. Since there were only 21 deaths from lung cancer, Sorahan and Lancashire (1997) state that it is impossible to determine which of the following three hypotheses is the correct one: (1) cadmium oxide in the presence of arsenic trioxide is a human lung carcinogen, (2) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (i.e., cadmium sulphate and cadmium sulphide were the main cadmium compounds of exposure when arsenic was not present), or (3) arsenic trioxide is a human carcinogen and the three cadmium compounds are not carcinogenic.

The carcinogenicity of cadmium has also been examined in European alloy, battery, smelter, and process workers. A study of workers at two copper-cadmium alloy facilities in the United Kingdom found no significant increase in lung cancer mortality (Sorahan et al. 1995). Dividing the workers into groups based on cumulative cadmium exposure or time since first exposure did not result in significant increases in lung cancer deaths in the alloy workers. An initial study of workers at nickel-cadmium battery

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manufacturing facilities in the United Kingdom found a significant increase in cancer of the respiratory tract (Sorahan and Waterhouse 1983). A subsequent study (Sorahan 1987) found an increase in lung cancer deaths among workers with the highest exposure first employed between 1926 and 1946; no association was found in workers employed after 1946. Another study of nickel-cadmium battery workers in the United Kingdom did not find significant increases in lung cancer deaths (Sorahan and Esmen 2004), although a significant increase in pharyngeal cancer deaths was observed. A study of nickel cadmium battery workers in Sweden found an increase in lung cancer mortality, but the increase was not statistically significant (Elinder et al. 1985c). An update of this study, which includes additional workers, found a significant increase in lung cancer deaths (Järup et al. 1998a). However, there was no exposure-response relationship between cumulative exposure to cadmium (or nickel) and the risk of lung cancer. A significant increase in lung cancer mortality was observed in workers employed at a zinc-lead-cadmium smelter (Ades and Kazantzis 1988). However, no relationship between cumulative cadmium exposure and lung cancer deaths was found, suggesting that cadmium was not the causative agent. Another study of workers in 19 facilities in the United Kingdom that process cadmium did not find a statistically significant increase in lung cancer deaths (Armstrong and Kazantzis 1983). An update of this study found a significant increase in lung cancer deaths (Kazantzis et al. 1988). However, >60% of the lung cancer deaths were workers at the zinc-lead-cadmium smelter examined by Ades and Kazantzis (1988).

Studies in rats provide strong evidence of the lung carcinogenic potential of chronically inhaled cadmium. Oldiges et al. (1989) reported a clear dose response increase in lung tumors in male and female rats from an 18-month continuous exposure to either cadmium chloride, cadmium oxide dusts, cadmium oxide fume, cadmium sulfate, or cadmium sulfide. In the cadmium chloride study at $30 \mu\text{g}/\text{m}^3$, the observation period in the males had to be shortened to 30 months (rather than 31) because of mortality in excess of 75%. No lung tumors were observed in control rats after 31 months of observation. A high incidence of nodules and tumors was seen in $30 \mu\text{g}/\text{m}^3$ exposures to cadmium chloride in both males and females. Results showed lung nodules in 18 of 20 males and 15 of 18 females and primary lung tumors in 15 of 20 males and 13 of 18 females. Tumor incidence as bronchioalveolar adenomas, adenocarcinomas, squamous cell carcinomas, or combined epidermoid carcinoma and adenocarcinoma were 2, 12, 0, and 1 for males; and 4, 7, 0, and 2 for females, respectively. Increased lung tumors in males and females were also observed with chronic exposures to cadmium oxide dust or fume at $30 \mu\text{g}/\text{m}^3$, to cadmium sulfate at $90 \mu\text{g}/\text{m}^3$, and to cadmium sulfide at $90 \mu\text{g}/\text{m}^3$ (Oldiges et al. 1989). Cadmium sulfate produced by photolysis of cadmium sulfide under the experimental conditions may have contributed to some of the response observed with cadmium sulfide (Konig et al. 1992).

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Takenaka et al. (1983) also demonstrated cadmium carcinogenicity in male rats exposed to cadmium chloride aerosols at 0.0134, 0.0257, and 0.0508 mg Cd/m³ for 18 months. The exposure produced a dose-related increase in lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas starting at 20 months. No other type of tumor was observed to increase with increasing dose.

In a protocol similar to the studies by Oldiges et al. (1989), Heinrich et al. (1989) did not observe an increase in lung tumors in male or female Syrian golden hamsters from chronic inhalation exposure to either cadmium oxide dust or fumes, cadmium chloride, cadmium sulfate, or cadmium sulfide. In female mice, lung tumor incidence increased at all dose levels, but incidence in the controls was also high, and the cadmium-induced increases were not statistically significant. Lung tumors in the cadmium-treated mice also did not increase in a dose-responsive manner except for a weak increase from exposure to the cadmium oxide fumes (Heinrich et al. 1989).

The available data provide inconclusive evidence on the potential of cadmium to induce lung cancer in humans. The strongest evidence comes from early studies of workers at a U.S. cadmium recovery facility (Stayner et al. 1992a; Thun et al. 1985), but later examinations of this cohort did not find conclusive evidence (Lamm et al. 1992, 1994; Sorahan and Lancashire 1997). The inconsistent results may be due to the small number of lung cancer cases and adjustments for possible early exposure to arsenic. Some studies of European cadmium workers have found significant increases in lung cancer (Ades and Kazantzis 1988; Järup et al. 1998a; Kazantzis et al. 1988; Sorahan 1987; Sorahan and Waterhouse 1983), but lung cancer deaths were not significantly associated with cumulative cadmium levels or duration of exposure and the investigators concluded that the effects may not have been related to cadmium exposure. Based on an early 1990s analysis of the available human and animal data, IARC (1993) classified cadmium as carcinogenic to humans (Group 1), based on sufficient evidence for carcinogenicity in both human and animal studies. Similarly, the DHHS (NTP 2011) classified cadmium and certain cadmium compounds as substances known to be human carcinogens. EPA classified cadmium as a probable human carcinogen by inhalation (Group B1), based on limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats (IRIS 2012). EPA estimated an inhalation unit risk (the risk corresponding to lifetime exposure to 1 µg/m³) of 1.8×10^{-3} based on the Thun et al. (1985) study (IRIS 2012). A range of concentrations that correspond to upper bound lifetime excess risks of 10^{-4} – 10^{-7} is shown in [Figure 3-1](#).

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3.2.2 Oral Exposure

Information on health effects of oral exposure to cadmium in humans is derived mainly from studies of residents living in cadmium-polluted areas. Cadmium exposure in these populations is often estimated by blood or urinary cadmium levels (see Section 3.8.1). Exposure in these cases occurs primarily through the diet, but smokers in these cohorts are also exposed to cadmium by inhalation. When evaluating oral exposure studies, smoking was treated as a confounding variable rather than an exposure route because of the large number of toxic compounds (in addition to cadmium) present in cigarette smoke, and because the primary concern is effects attributable to cadmium. Cadmium is more readily found in the free ionic form in water, while in food, the cadmium ion generally exists in a complex with a variety of ligands, including proteins such as metallothionein (Crews et al. 1989; Groten et al. 1990; Nordberg et al. 1986). Experimental studies in animals have generally used soluble salts of cadmium (such as cadmium chloride) for food, drinking water, and gavage exposures. The toxicological properties of the cadmium ion do not appear to depend on the counter ion, although absorption may be significantly affected by protein complexes (see Section 3.3.1.2).

3.2.2.1 Death

Intentional ingestion of cadmium has been used as a means of suicide, causing death due to massive fluid loss, edema, and widespread organ destruction (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). The doses ingested in two known fatal cases were estimated to be 25 mg Cd/kg from cadmium iodide (Wisniewska-Knypl et al. 1971) and 1,840 mg Cd/kg from cadmium chloride (Buckler et al. 1986). Time to death after cadmium iodide ingestion was 7 days (Wisniewska-Knypl et al. 1971) and 33 hours after ingestion of the cadmium chloride (Buckler et al. 1986).

In rats and mice, acute oral LD₅₀ (lethal dose, 50% kill) values for cadmium range from about 100 to 300 mg/kg (Baer and Benson 1987; Basinger et al. 1988; Kostial et al. 1978; Kotsonis and Klaassen 1978; Shimizu and Morita 1990). The lowest dose causing death (2 of 20 animals) was 15.3 mg/kg in Sprague-Dawley rats (Borzelleca et al. 1989). Very young animals have lower LD₅₀ values than adult animals (Kostial et al. 1978, 1989); this effect may be related to the greater fractional absorption of ingested cadmium in the immature organism (see Section 3.4.1.2). For example, the LD₅₀ values in rats aged 2, 3, 6, 18, and 54 week are 47, 240, 216, 170, and 109 mg/kg, respectively (Kostial et al. 1978).

Deaths related to cadmium exposure have been reported in only two of the intermediate exposure studies found. In a study in Wistar rats exposed to cadmium chloride by gavage at 40 mg Cd/kg/day,

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5 days/week for up to 14 weeks; 4 of 13 female Wistar rats died by 8 weeks (Baranski and Sitarek 1987). In mice, Blakley (1986) studied the effect of cadmium on chemical- and viral-induced tumor production. Female albino Swiss mice (8 weeks old, n=41) were administered cadmium chloride in the drinking water for 280 days at doses of 0, 5, 10, or 50 ppm. These mice have a high incidence of spontaneous lymphocytic leukemia of thymic origin. A significant 33% increase ($p=0.0228$, chi-square analysis) in deaths from virally induced leukemia was observed from exposure to 1.9 or 9.5 mg Cd/kg/day. The deaths were attributed to cadmium-impaired immunosurveillance mechanisms that control expression of the murine lymphocytic leukemia virus.

The LOAEL values from each reliable study for lethality in each species and duration category are recorded in [Table 3-6](#) and plotted in [Figure 3-2](#).

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in [Table 3-6](#) and plotted in [Figure 3-2](#).

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to cadmium.

No respiratory effects were observed in Rhesus monkeys from 4 mg/kg/day of cadmium chloride in the food for 9 years (Masaoka et al. 1994). Intermediate-duration oral exposure caused fibrosis in lungs of rats exposed to 2.4 mg Cd/kg/day of cadmium chloride after 6 and 16 weeks (Miller et al. 1974b). Petering et al. (1979) observed a reduced static compliance and lung lesions (not specified) in male Sprague-Dawley rats exposed to 1.2 mg Cd/kg/day in water for 200 days. Zinc-deficient rats were more susceptible to lung lesions from exposure to cadmium chloride (Petering et al. 1979). Rats exposed to cadmium chloride at 3.62 mg Cd/kg/day in the drinking water for 120 days developed emphysema (Petering et al. 1979). No histopathologic lesions of the lung were found in male Sprague-Dawley rats after 24 weeks of exposure to cadmium in drinking water at a maximum dose of 8 mg/kg/day (Kotsonis and Klaassen 1978). Lung weight was unchanged in Wistar rats after 90 days of exposure in drinking water at 16 mg/kg/day (Prigge 1978a). Effects on the lung following oral exposure to cadmium may be secondary to systemic changes (Petering et al. 1979); however, the studies that found lung effects did not examine other systemic effects in the exposed rats (Miller et al. 1974b; Petering et al. 1979).

Table 3-6 Levels of Significant Exposure to Cadmium - Oral

Key to Figure ^a	Species (Strain)	Exposure/Duration/ Frequency (Route)	System	LOAEL			Reference	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (NS)	once (G)				29 (LD50 at 8 days; 2 weeks old)	Kostial et al. 1978 CdCl2	
						129 F (LD50 at 8 days; 6 weeks old)		
						104 F (LD50 at 8 days; 18 weeks old)		
2	Rat (Sprague-Dawley)	once (GW)				225 M (LD50 at 14 days)	Kotsonis and Klaassen 1977 CdCl2	
3	Rat (Sprague-Dawley)	2 wk (W)				42 M (7/9 died within 2 weeks)	Kotsonis and Klaassen 1978 CdCl2	
4	Rat (Sprague-Dawley)	once (GW)				327 M (LD50 at 24 hours; fed rats)	Shimizu and Morita 1990 CdCl2	
						107 M (LD50 at 24 hours; fasted rats)		
5	Mouse (Swiss-Webster)	once (GW)				95.5 M (LD50 at 96 hours)	Baer and Benson 1987 CdCl2	
6	Mouse (ICR)	once (GW)				112 M (5/10 died within 8 days)	Basinger et al. 1988 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference	Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)			
Systemic									
7	Rat (Wistar)	10 d Gd 7-16 once (GW)	Bd Wt	2 F	12 F (14% decreased maternal body weight)		Baranski 1985	CdCl2	
8	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Hemato	31.3 M 138 F	65.6 M (increased hemoglobin, hematocrit, erythrocytes)		Borzelleca et al. 1989	CdCl2	
			Hepatic	65.6 M		138 M (focal necrosis of hepatocytes)			
			Renal			15.3 (focal necrosis of tubular epithelium)			
			Bd Wt		15.3 M (18% decreased body weight)	31.3 M (23% decreased body weight)			
				31.3 F	65.6 F (18% decreased body weight)				
9	Rat (Sprague-Dawley)	10 d (W)	Hepatic	13.9			Borzelleca et al. 1989	CdCl2	
			Renal	13.9					
			Bd Wt	13.9					
				1.1 M	7.8 M (14% decreased body weight)	11.2 M (25% decreased body weight)			

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
10	Rat (Sprague-Dawley)	once (GW)	Cardio	150 M			Kotsonis and Klaassen 1977 CdCl ₂	
			Hemato	150 M				
			Hepatic	150 M				
			Renal		25 M (50% decrease in urine flow for first 2 days)			
			Bd Wt	100	150 M (initial 12% decreased body weight)			
11	Rat (Long-Evans)	Gd 6-15 (GW)	Gastro	6.13 F		61.32 F (intestinal necrosis, hemorrhage, ulcers)	Machemer and Lorke 1981 CdCl ₂	
			Bd Wt	1.84 F	6.13 F (27% decrease in body weight gain during treatment)	18.39 F (persistent 50% decrease in maternal body weight gain)		
12	Rat (Long-Evans)	Gd 6-15 (F)	Gastro	12.5 F			Machemer and Lorke 1981 CdCl ₂	
			Bd Wt	3.5 F	12.5 F (transient 19% decrease in maternal body weight gain during treatment)			
13	Rat (Wistar)	12 d (W)	Hemato		12 M (anemia)		Sakata et al. 1988 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
14	Rat (Sprague-Dawley)	once (GW)	Hepatic		75 M (focal degeneration and necrosis of parenchymal cells)		Shimizu and Morita 1990 CdCl ₂	
15	Mouse (CBA/Bom)	once (GW)	Gastro	15.7 M	30.4 M (gastritis and enteritis)	88.8 M (severe gastric necrosis)	Andersen et al. 1988 CdCl ₂	
			Hepatic	15.7 M	30.4 M (fatty infiltration of liver cells, occasional hepatocellular necrosis)			
			Renal	59.6		88.8 M (tubular necrosis and casts)		
16	Mouse (ICR)	once (GW)	Gastro			112 M (glandular stomach epithelial necrosis)	Basinger et al. 1988 CdCl ₂	
			Hepatic			112 M (extensive hepatocellular coagulative necrosis)		
Immuno/ Lymphoret								
17	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Renal	112 M			Borzelleca et al. 1989 CdCl ₂	
				65.6 M 31.3 F	65.6 F (increased leukocyte counts)			
Neurological								
18	Rat (Sprague-Dawley)	once (GW)		25 M	50 M (decreased motor activity)		Kotsonis and Klaassen 1977 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive							
19 Rat (Wistar)	once (GW)		50 M		100 M (testicular necrosis)	Bomhard et al. 1987 CdCl2	
20 Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F		65.6 M (testicular atrophy and loss of spermatogenic elements)	Borzelleca et al. 1989 CdCl2	
21 Rat (Sprague-Dawley)	once (GW)		25 M			Dixon et al. 1976 CdCl2	
22 Rat (Sprague-Dawley)	once (GW)		50 M		100 M (testicular necrosis; decreased spermatogenesis; decreased number females producing pups)	Kotsonis and Klaassen 1977 CdCl2	
23 Mouse (CBM/ Bom)	once (GW)		30.3 M		59.6 M (testicular necrosis)	Andersen et al. 1988 CdCl2	
Developmental							
24 Rat (Wistar)	10 d Gd 7-16 once (GW)			2 F (delayed ossification of the sternum and ribs)	40 (fused lower limbs, absent limbs, decreased number of live fetuses, increased number of resorptions)	Baranski 1985 CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
25	Rat (Long- Evans) 1 x/d Gd 6-15 (GW)		6.13		18.39 (increased number of fetuses with malformations)	Machemer and Lorke 1981 CdCl2	
26	Rat (Long- Evans) 10 d Gd 6-15 (F)		12.5			Machemer and Lorke 1981 CdCl2	
INTERMEDIATE EXPOSURE							
27	Rat (Wistar) 14 wk 5 d/wk (GW)				40 F (4/13 died by week 8; 7/13 by week 14)	Baranski and Sitarek 1987 CdCl2	
28	Mouse (Swiss) 280 d (W)				1.9 F (24/41 died by 280 days)	Blakley 1986 CdCl2	
Systemic							
29	Monkey (Rhesus) 10 wk (F)	Bd Wt	5 M			Chopra et al. 1984 CdCl2	
30	Rat (Wistar) 14 wk 5 d/wk (GW)	Bd Wt	4 F		40 F (29% decreased maternal body weight)	Baranski and Sitarek 1987 CdCl2	
31	Rat (Sprague-Dawley) 2-10 mo (W)	Renal			30 F (B2-microglobulinuria)	Bernard et al. 1988a CdCl2	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
32	Rat (Wistar)	daily 12 mo (W)	Musc/skel	0.2 M	0.5 M (increased lumbar spine deformities, decreased in lumbar spine and femur mineralization, altered bone turnover parameters)		Brzoska and Moniuszko-Jakoniuk 2005a, 2005b; Brzoska et al. 2010 CdCl ₂	
33	Rat (Wistar)	daily 12 mo (W)	Musc/skel		^b 0.2 F (decreased bone mineralization, mechanical properties of tibia and femur, and altered bone turnover parameters)		Brzoska and Moniuszko-Jakoniuk 2005d; Brzoska et al. 2005a, 2005c CdCl ₂	
34	Rat (Wistar)	daily 12 mo (W)	Musc/skel		0.3 F (alterations in bone mineral content and density and mechanical properties of lumbar vertebral and femoral bones)		Brzoska et al. 2004b, 2005b CdCl ₂	
35	Rat (Sprague-Dawley)	4 or 7 mo (W)	Renal			15.2 F (albuminuria, transferrinuria, B2-microglobulinuria)	Cardenas et al. 1992a CdCl ₂	
36	Rat (Sprague-Dawley)	190 d (W)	Cardio		1.4 M (20% increase in diastolic blood pressure)		Carmignanti and Boscolo 1984 Cd acetate	
			Bd Wt	2.8 M				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
37	Rat (Sprague- Dawley)	12 wk (W)					
		Hepatic		8.58 M (necrosis of central lobules)		Cha 1987 CdCl ₂	
		Renal		8.58 M (necrosis of proximal tubular epithelial cells and cloudy swelling)			
		Bd Wt		8.58 M (23% decreased in body weight gain; 9% total body weight decrease)			
38	Rat (Wistar)	170 d (W)	56 F			Cifone et al. 1989a CdCl ₂	
39	Rat (Sprague- Dawley)	3 mo (W)		2 (anemia)		Decker et al. 1958 CdCl ₂	
		Hemato					
		Bd Wt		2 F (15% decreased body weight)	2 M (25% decreased body weight)		
40	Rat (Wistar)	4-60 wk (W)		1.18 (vesiculation of proximal tubules)		Gatta et al. 1989 CdCl ₂	
41	Rat	4 wk (F)		2.5 M (anemia)		Groten et al. 1990 CdCl ₂	
		Hemato					
		Renal	2.5 M				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
42	Rat (Wistar)	Hemato		3.6 M (anemia)		Itokawa et al. 1974 CdCl ₂	
		Renal		3.6 M (tubular necrosis and casts, glomerular adhesions)			
43	Rat (Sprague- Dawley)	Cardio			2.5 M (congested myocardium, separation of muscle fibers)	Jamall et al. 1989 CdCl ₂	
		Renal	2.5 M				
		Bd Wt	2.5 M				
		Hemato		8 F (anemia)			Kawamura et al. 1978 CdCl ₂
44	Rat (Wistar)	Musc/skel		8 F (osteomalacia changes)			
		Renal		8 F (decreased renal clearance)			
		Endocr	8 F				
		Bd Wt		8 F (12% decreased body weight)			
		Hemato		1.5 F (slight anemia)			Keiman et al. 1978 form not specified
		Musc/skel	3.8 F				
45	Rat (Sprague- Dawley)	Hemato					

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
46	Rat (Sprague-Dawley)	24 wk (W)	Resp	8 M				Kotsonis and Klaassen 1978 CdCl ₂	
			Cardio	8 M					
			Gastro	8 M					
			Hemato	8 M					
			Musc/skel	8 M					
			Hepatic	8 M					
			Renal	1.2 M			3.1 M (proteinuria, slight focal tubular necrosis)		
47	Rat (Wistar)	8 weeks daily (W)	Endocr	8 M				Larregle et al. 2008 CdCl ₂	
			Bd Wt	8 M					
			Hepatic		18 M (increased serum and liver triglyceride levels; increased serum cholesterol levels)				
48	Rat (Wistar)	3 mo (F)	Cardio	3				Loeser and Lorke 1977a CdCl ₂	
			Hemato	3					
			Hepatic	3					
			Renal	3					
			Endocr	3					
			Bd Wt	3					

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
49	Rat (Sprague- Dawley)	6-16 wk (W)			2.4 (lung fibrosis)	Miller et al. 1974b CdCl ₂	
50	Rat (Sprague- Dawley)	6 wk 5 d/wk 1 x/d (GW)	0.25 M			Muller et al. 1988 Cd acetate	
51	Rat (NS)	4 wk (W)	0.25 M			Ogoshi et al. 1989 CdCl ₂	
				0.8 F (decreased hematocrit and hemoglobin)			
				0.8 F (decreased bone strength in young animals)			
				1.6 F (10% decreased body weight gain)			
52	Rat (NS)	200 d (W)	0.6 M	1.2 M (reduced static compliance, lung lesions)		Petering et al. 1979 CdCl ₂	
53	Rat (Sprague- Dawley)	120 d (W)			3.62 M (emphysema)	Petering et al. 1979 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure ^a (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
54	Rat (Sprague-Dawley) 111 d (90 d prior to Gd 1-21) (W)	Hemato	5.23 F			Petering et al. 1979 CdCl ₂	
55	Rat (Sprague-Dawley) Gd 1- Ld 1 (F)	Bd Wt			19.7 F (77-80% decreased maternal weight gain)	Pond and Walker 1975 CdCl ₂	
56	Rat (Wistar) 90 d (W)	Resp	16 F			Prigge 1978a CdCl ₂	
		Hemato		4 F (23% decreased serum iron)			
		Renal	4 F	8 F (35% increase in urine protein)			
		Bd Wt	8 F				
57	Rat (Wistar) 12, 26, 50, or 100 d (W)	Hemato			12 M (iron deficient anemia)	Sakata et al. 1988 CdCl ₂	
58	Rat (Sprague-Dawley) 7-12 mo (W)	Renal	13 F			Viau et al. 1984 CdCl ₂	
		Bd Wt	13 F				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
59	Mouse (CF1)	Musc/skel		0.65 F (decrease in femur calcium content in mice undergoing repeated pregnancy/lactation periods)		Bhattacharyya et al. 1988a, 1988b	
60	Mouse (C57BL/6)	Bd Wt			12.5 M (63% decreased body weight gain)	Malave and de Ruffino 1984	
61	Mouse (B6C3F1)	Bd Wt			232 M (45% decreased body weight)	Waalkes et al. 1993	
62	Mouse (QS/CH)	Hemato	4.8 F	9.6 F (anemia)		Webster 1978	
		Bd Wt	4.8 F	9.6 F (14% decrease in maternal weight gain)		CdCl2	
63	Dog (Beagle)	Cardio	0.75			Loeser and Lorke 1977b	
		Hemato	0.75				
		Hepatic	0.75				
		Renal	0.75				
		Bd Wt	0.75				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
				Less Serious (mg/kg/day)	Serious (mg/kg/day)			
64	Rabbit (New Zealand)	Cardio		1.6 M (increased aortic resistance, reduced contractility)		Boscolo and Carmignani 1986 CdCl2		
		Renal	1.6 M					
		Bd Wt	1.6 M					
		Hemato		14.9 M (anemia)				
65	Rabbit (New Zealand (W) and Belgian Giant)	Hepatic		14.9 M (focal hepatic fibrosis and biliary hyperplasia)		Stowe et al. 1972 CdCl2		
		Renal			14.9 M (tubular necrosis, glomerular and interstitial fibrosis)			
		Endocr	14.9					
		Bd Wt		14.9 M (11% decrease in body weight)				
Immuno/ Lymphoret								
66	Monkey (Rhesus)	10 wk (F)		5 M (increased cell-mediated immune response)		Chopra et al. 1984 CdCl2		
67	Rat (Wistar)	170 d (W)		28 F (biphasic decrease then increase in natural killer cell activity)		Cifone et al. 1989a CdCl2		

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
68	Rat (Wistar)	3 mo (F)	3			Loeser and Lorke 1977a CdCl ₂	
69	Mouse (BDF1)	3 wk (W)	1.4 F	2.8 F (decreased humoral immune response)		Blakley 1985 CdCl ₂	
70	Mouse (Swiss)	280 d (W)		1.9 F (greater susceptibility to murine lymphocytic leukemia virus)		Blakley 1986 CdCl ₂	
71	Mouse (BDF1)	26 d (W)	12.5 F			Blakley 1988 CdCl ₂	
72	Mouse (Swiss- Webster)	30 d (W)	22 M			Bouley et al. 1984 Cd acetate	
73	Mouse (Swiss- Webster)	10 wk (W)	57 M			Exon et al. 1986 CdCl ₂ , Cd acetate, or Cd sulfate	
74	Mouse (C57BL/6N)	12-16 wk (W)	19 F	57 F (reduced number of SRBC-activated, plaque-forming cells)		Krzyszyniak et al. 1987 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
75	Mouse (C57BL/6)	3-11 wk (W)		12.5 M (decreased suppressor cell activity)		Malave and de Ruffino 1984 CdCl ₂	
76	Mouse (ICR)	10 wk (W)		0.75 M (induction of anti-nuclear autoantibodies)		Ohsawa et al. 1988 CdCl ₂	
Neurological							
77	Rat (Wistar)	14 wk 5 d/wk (GW)	4 F	40 F (aggressive behavior)		Baranski and Sitarek 1987 CdCl ₂	
78	Rat (Sprague- Dawley)	3-24 wk (W)	1.2 M	3.1 M (decreased motor activity)		Kotsonis and Klaassen 1978 CdCl ₂	
79	Rat (Sprague- Dawley)	55 d (F)	1 M	5 M (increased passive avoidance)		Nation et al. 1984 CdCl ₂	
80	Rat (Sprague- Dawley)	60 d (F)		9 M (decreased motor activity)		Nation et al. 1990 CdCl ₂	
Reproductive							
81	Rat (Wistar)	14 wk 5 d/wk (GW)	4 F	40 F (increased duration of estrus cycle)		Baranski and Sitarek 1987 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
82	Rat (Wistar)	11 wk 5 d/wk (GW)	4 F			Baranski et al. 1983 CdCl ₂	
83	Rat (Wistar)	10 wk 1 x/wk (GW)	5 M			Bomhard et al. 1987 CdCl ₂	Histopathology only.
84	Rat (Sprague- Dawley)	12 wk (W)		8.58 M (necrosis and atrophy of seminiferous tubule epithelium)		Cha 1987 CdCl ₂	
85	Rat	4 wk (F)	2.5 M			Groten et al. 1990 CdCl ₂	Histopathology only.
86	Rat (albino)	4 wk (W)	4.8 F			Kostial et al. 1993 CdCl ₂	
87	Rat (Sprague- Dawley)	24 wk (W)	8 M			Kotsonis and Klaassen 1978 CdCl ₂	
88	Rat (Wistar)	3 mo (F)	3			Loeser and Lorke 1977a CdCl ₂	Histopathology only.
89	Rat (NS)	120 d (W)		12.6 M (decreased sperm count and motility, seminiferous tubular damage)		Saxena et al. 1989 Cd acetate	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)			
90	Rat (Long-Evans) (W)	70-80 d	4.64 M				Zenick et al. 1982 CdCl ₂	
91	Dog (Beagle)	3 mo (F)	0.75				Loeser and Lorke 1977b CdCl ₂	
Developmental								
92	Rat (Wistar)	21 d Gd 1-21 (W)		0.706	(delayed development of sensory motor coordination reflexes; increased motor activity)		Ali et al. 1986 Cd acetate	
93	Rat (Wistar)	20 d Gd 1-20 (W)		9.6	(decreased fetal body weight [12%], body length [7%], and hematocrit [13%])		Baranski 1987 CdCl ₂	Decreased maternal water and food consumption.
94	Rat (Wistar)	11 wk 5 d/wk 1 x/d (GW)		0.04	(pup behavioral alterations)		Baranski et al. 1983 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg)	Serious (mg/kg)		
95	Rat (Wistar) 11-94 d Gd 5-15 Ld 2-28 1 x/d ppd 1-56 5 d/wk 1 x/d (GW)			14 M (decreased horizontal ambulation and rearing activity; increased frequency of somatosensory, visual, and auditory electrocorticogram; prolonged latency and duration of evoked potentials)		Desi et al. 1998 CdCl ₂	
96	Rat (Druckery) Gd 0- Ld 21 (W)			5 (decreased pup brain and body weight at 7, 14, and 21 days)		Gupta et al. 1993 Cd acetate	
97	Rat (Sprague- Dawley) Gd 0-20 (W)			1.5 (12% decreased hematocrit)		Kelman et al. 1978 form not specified	
98	Rat (albino) 10 wk (W)			4.8 (12% decrease in pup body weight at weaning)		Kostial et al. 1993 CdCl ₂	
99	Rat (Wistar) approx. 49 d 4 wk old through mating 7 d/wk 1 x/d (GO)			7 M (alterations in ambulation behavior; prolonged latency and duration of somatosensory evoked potentials)		Nagymajtenyi et al. 1997 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
100	Rat (Sprague- Dawley)	60 d prior to Gd 1 or Gd 1-21 (W)		2.61 (decreased live birth weight)		Petering et al. 1979 CdCl ₂	
101	Rat (Sprague- Dawley)	Gd 1- Ld 1 (F)		19.7 (13-19% decreased pup birth weight)		Pond and Walker 1975 CdCl ₂	
102	Rat (ITRC)	21 d Gd 0-20 (W)	21			Saxena et al. 1986 Cd acetate	
103	Rat (Sprague- Dawley)	15 d Gd 6-20 (W)	0.63	4.7 (8% decreased fetal body weight)		Sorell and Graziano 1990 CdCl ₂	
104	Rat (Sprague- Dawley)	9 wk 1 x/d (GW)	1	10 (delayed ossification, decreased body weight)		Sutou et al. 1980 form not specified	
105	Mouse (QS/CH)	19 d Gd 1-19 (W)		2.4 (decreased fetal body weight; severe anemia)		Webster 1978 CdCl ₂	
CHRONIC EXPOSURE							
Systemic							
106	Human	Renal	0.0003 F ^c			Buchet et al. 1990; Jarup et al. 2000; Suwazono et al. 2006 form not specified	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
107	Human	NS lifetime (F)	Renal	0.0021			Nogawa et al. 1989	form not specified
108	Human	>25 yr lifetime (environ)	Hemato	0.0078			Shiwen et al. 1990	Cd metal
			Musc/skel	0.0078				
			Renal		0.0078	(increased excretion of low molecular weight proteins)		
109	Monkey (Rhesus)	9 yr (F)	Cardio	0.53 M	1.71 M	(increased blood pressure during the first 1.5 years)	Akahori et al. 1994	CdCl ₂
110	Rat (Sprague-Dawley)	18 mo (W)	Renal			13 F (loss of glomerular polyanion charge barrier, proteinuria)	Bernard et al. 1992	CdCl ₂
111	Rat (Wistar)	72 wk (F)	Renal	3.5	17.5	(8 to 9-fold increase in LDH and GST starting at 13 weeks)	Bomhard et al. 1984	CdCl ₂

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
112 Rat (Wistar)	daily 24 mo (W)	Musc/skel		0.08 F (decreases in bone mineral content and density of lumbar spine, altered bone turnover parameters, increases in deformed and fractured vertebral bodies)		Brzoska and Moniuszko-Jakoniuk 2004a, 2004b; Brzoska 2011 CdCl ₂	
113 Rat (Sprague-Dawley)	12 mo (W)	Hemato	0.79			Decker et al. 1958 CdCl ₂	
		Bd Wt	0.79				
114 Rat (Sprague-Dawley)	M: 92 wk F: 84 wk (W)	Cardio	4.01			Fingerle et al. 1982 CdCl ₂	
		Renal	0.8	1.51 (proximal tubule lesions)			
		Bd Wt	4.01				
115 Rat (Sprague-Dawley)	6, 12, or 18 mo (W)	Cardio	2.281 F			Mangler et al 1988 CdCl ₂	
		Hepatic	2.281 F				
		Renal		2.337 F (cloudy swelling of tubular cells)			
		Bd Wt	2.281 F				

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
116	Rat (Wistar)	Musc/skel			3.6 (muscle atrophy)	Sato et al. 1978 CdCl ₂	
		Bd Wt	3.6				
117	Rat (Wistar)	Renal	2.6 M			Shaikh et al. 1989 CdCl ₂	
118	Rat (Wistar)	Bd Wt	3.5 M	7 M (10% decreased body weight)		Waalikes and Rehm 1992 CdCl ₂	
119	Mouse (CF1)	Musc/skel	0.65 F	6.5 F (loss of bone calcium in ovariectomized mice)		Bhattacharyya et al. 1988c	
120	Mouse (CBA/H)	Hemato			57 (anemia and bone marrow hypoplasia)	Hays and Margaretten 1985 form not specified	
		Renal	57				
Neurological 121	Rat (Wistar)	Bd Wt			57 (21% decreased terminal body weight)		
					3.6 (peripheral neuropathy)	Sato et al. 1978 CdCl ₂	

Table 3-6 Levels of Significant Exposure to Cadmium - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer							
122	Rat (Wistar)	77 wk (F)			3.5 M (CEL: increased rates of prostatic adenomas)	Waalikes and Rehm 1992 CdCl ₂	

a The number corresponds to entries in Figure 3-2.

b The intermediate-duration oral MRL of 0.0005 mg Cd/kg/day (0.5 ug Cd/kg/day) was calculated using a benchmark dose analysis. The BMDL 1std of 0.05 mg Cd/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability).

c The chronic-duration oral MRL of 0.0001 mg Cd/kg/day (0.1 ug Cd/kg/day) was calculated from the 95% lower confidence limit of the urinary cadmium level associated with a 10% increased risk of low molecular weight proteinuria (0.5 ug/g creatinine) estimated from a meta-analysis of select environmental exposure studies. An intake which would result in this urinary cadmium concentration was estimated using a modification of the Nordberg-Kjellström pharmacokinetic model (see Appendix A for details on the meta-analysis and extrapolation to dietary intake). This dose of 0.3 ug/kg/day was divided by an uncertainty factor of 3 for human variability.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; GST = glutathione-S-transferase; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LDH = Lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = post-parturition day; Resp = respiratory; SRBC = sheep red blood cells; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Cadmium - Oral

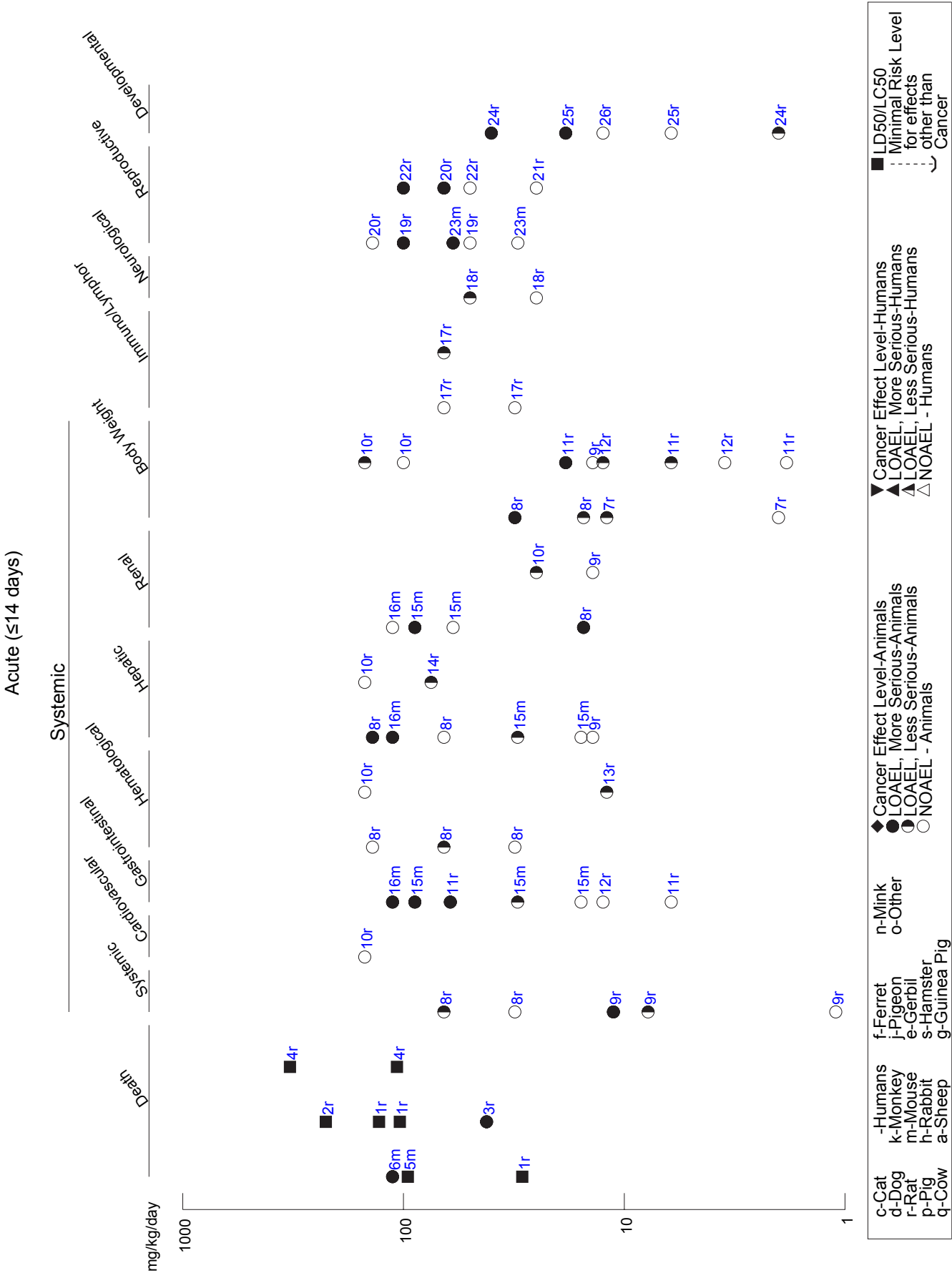


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral (Continued)

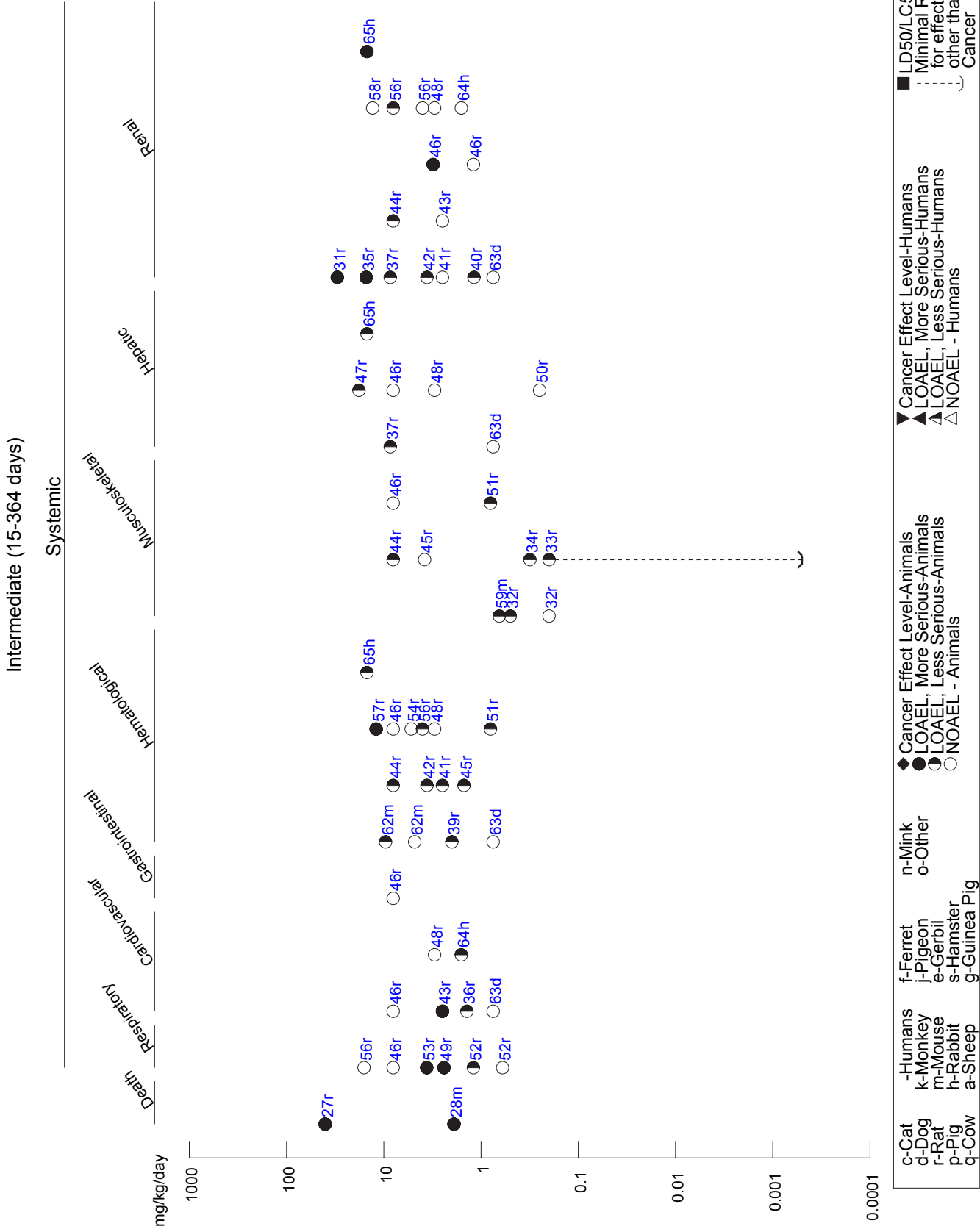


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral (Continued)

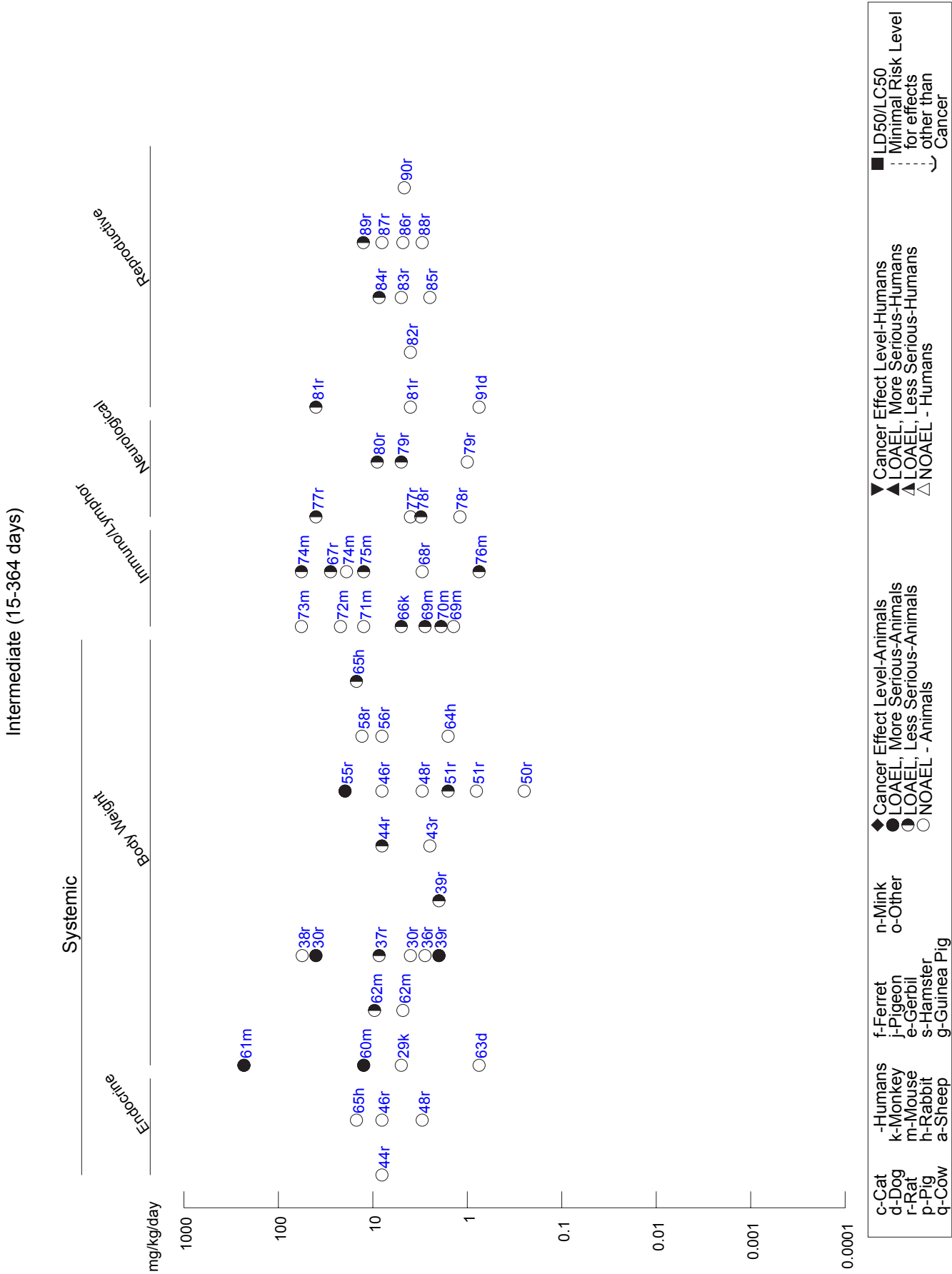


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral (Continued)

Intermediate (15-364 days)

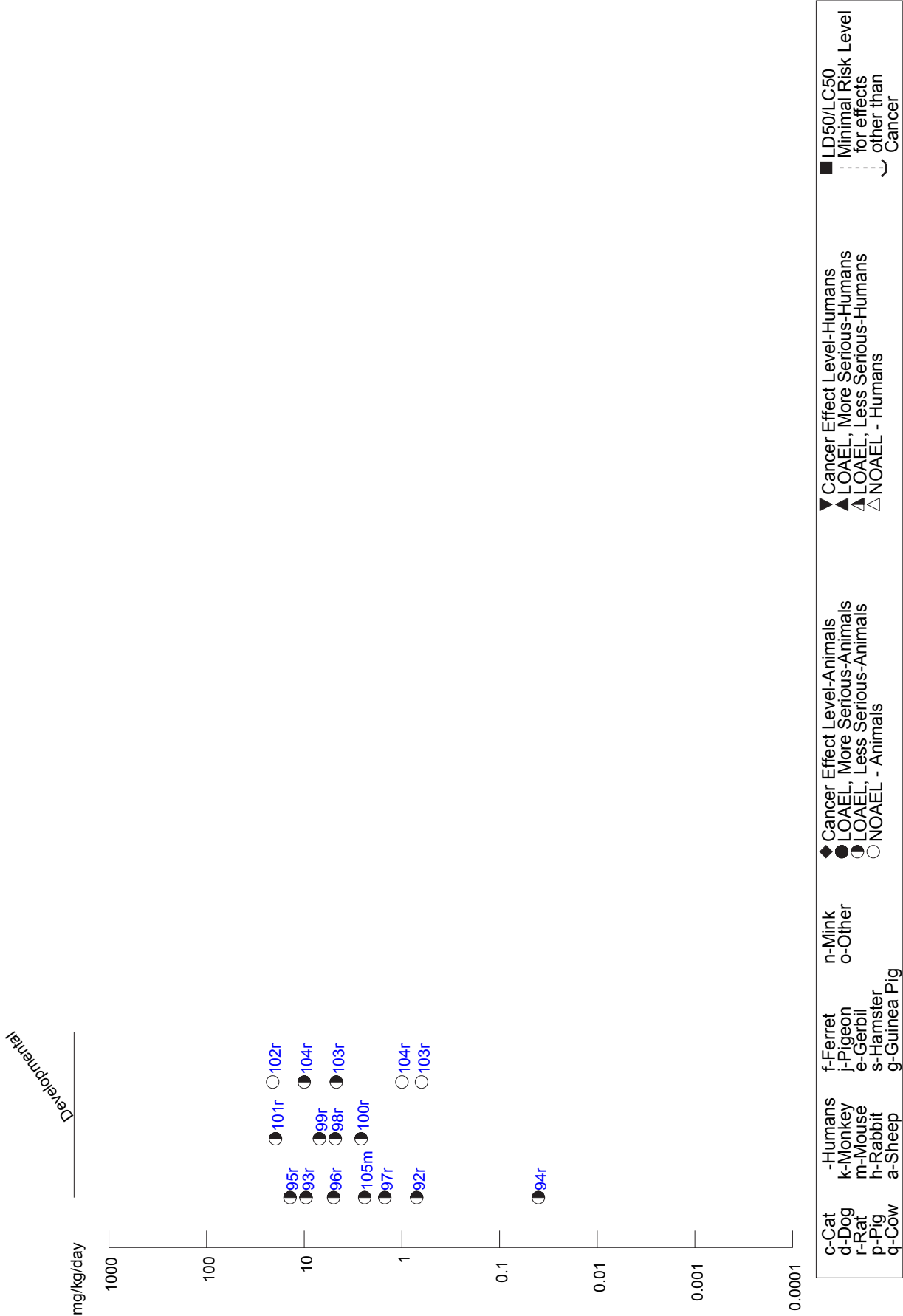
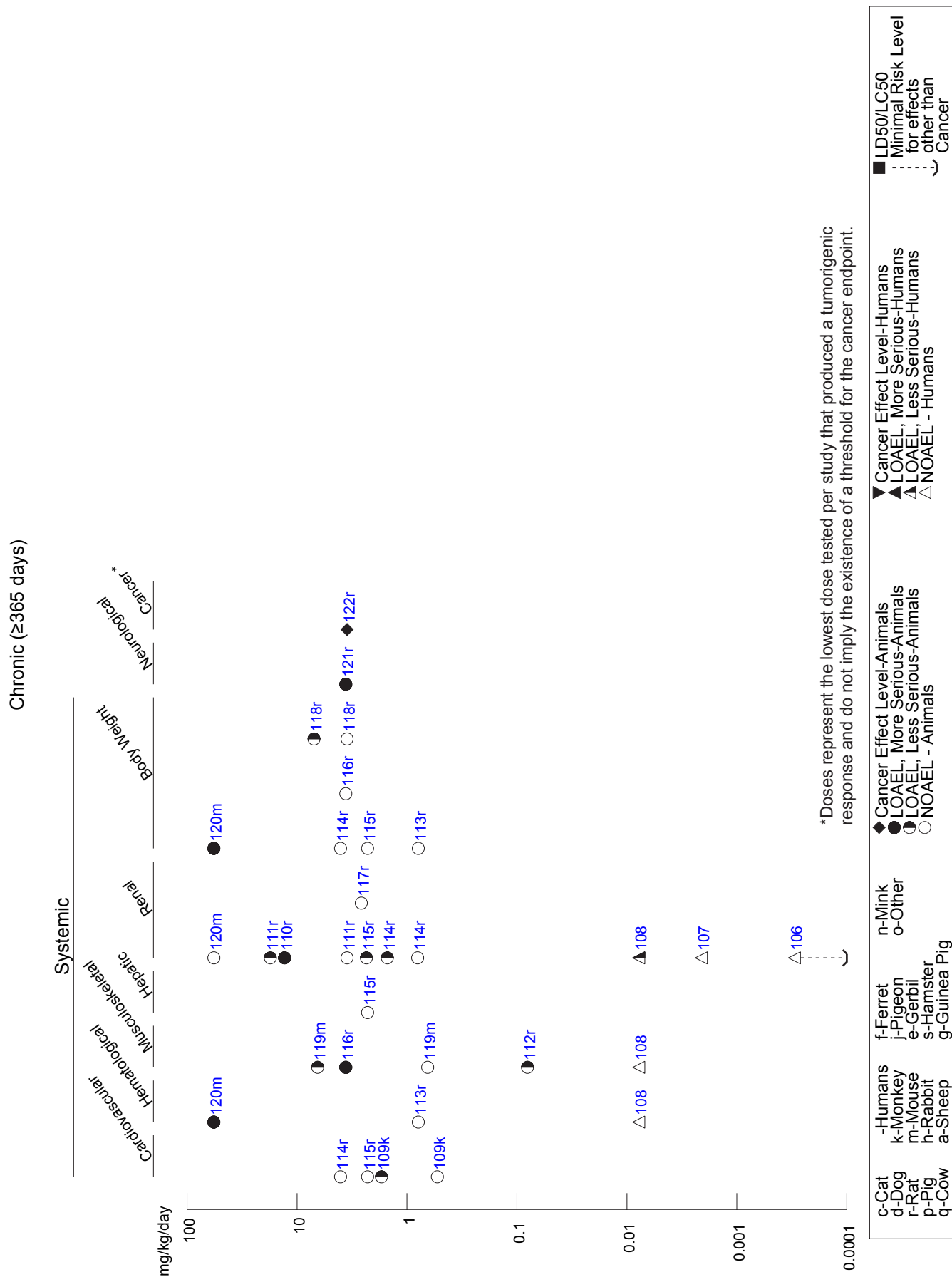


Figure 3-2 Levels of Significant Exposure to Cadmium - Oral (Continued)



3. HEALTH EFFECTS

Cardiovascular Effects. Studies regarding cardiovascular effects in humans after oral exposure to cadmium have primarily investigated relationships between blood pressure and biomarkers of cadmium exposure such as cadmium levels in blood, urine, or other tissues. Smoking is an important confounding factor, because of the higher blood, urine, and tissue cadmium levels of smokers (see Section 3.4) and the known cardiovascular toxicity of cigarette smoking. Case-control and cohort epidemiologic studies that adequately control for smoking have typically found no association between body cadmium levels (primarily reflecting dietary exposure) and hypertension (Beevers et al. 1980; Cummins et al. 1980; Ewers et al. 1985; Lazebnik et al. 1989; Satarug et al. 2005; Shiwen et al. 1990); however, some studies have found positive correlations (Geiger et al. 1989; Swaddiwuhipong et al. 2010; Tulley and Lehmann 1982) or negative correlations (Kagamimori et al. 1986; Staessen et al. 1984). Similar conflicting findings have been reported in studies analyzing death rates from cardiovascular disease among populations with dietary cadmium exposure (Inskip et al. 1982; Shigematsu 1984). Disorders of the cardiac conduction system, lower blood pressure, and decreased frequency of cardiac ischemic changes were found among elderly women with past high dietary exposure to cadmium (Kagamimori et al. 1986). Rhythmic disturbances, including ventricular fibrillation, were seen in an individual who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

Several studies conducting cross-sectional analysis on data from the National Health and Nutrition Examination Surveys (NHANES), investigated associations between blood and urine cadmium levels and cardiovascular effects (Agarwal et al. 2011; Eguogu et al. 2009; Everett and Frithsen 2008; Menke et al. 2009; Navas-Acien et al. 2005; Peters et al. 2010; Tellez-Plaza et al. 2008, 2010). Among adult participants in the NHANES 1988–1994 survey followed for mortality through 2000, the multivariable (including smoking)-adjusted hazard ratios of cardiovascular mortality associated with a 2-fold increase in creatinine-corrected urinary cadmium were 1.21 (95% CI of 1.07–1.36) in men and 0.93 (95% CI of 0.84–1.04) in women (Menke et al. 2009). The hazard ratios for coronary heart disease mortality were 1.36 (95% CI of 1.11–1.66) and 0.82 (95% CI of 0.76–0.89). Thus, the study suggests an association between elevated cadmium exposure and increased risk of cardiovascular mortality in men, but not in women. Urinary cadmium levels were found to be strongly associated with peripheral arterial disease (PAD, defined as blood pressure ankle brachial index <0.9 in at least one leg) in analysis conducted on 728 participants (at least 40 years of age) in the NHANES 1999–2000 study (Navas-Acien et al. 2005) and approximately 6,500 participants (≥40 years of age) in the NHANES 1999–2004 survey (Tellez-Plaza et al. 2010). Navas-Acien et al. (2005) reported that individuals with PAD had a 36% higher mean urine cadmium level than individuals without PAD; this study also found that individuals with PAD had 49%

3. HEALTH EFFECTS

higher urinary tungsten levels and urinary antimony levels exceeding 0.1 µg/L. In the Tellez-Plaza et al. (2010) analysis, the odds ratio for PAD comparing men with urinary cadmium levels in the highest quartile (≥ 0.69 µg/g creatinine) with the lowest quartile (< 0.20 µg/g creatinine) was 4.90 (95% CI of 1.55–15.54), after adjustment for age, race/ethnicity, education, smoking habits, and a variety of cardiovascular risk factors. In contrast, the odds ratio in women was 0.56 (95% CI of 0.18–1.71). When the women were divided by smoking habit, there was a positive progressive dose-response relationship and the odds ratio for PAD comparing the 80th with the 20th percentile for urinary cadmium was 1.46 (95% CI of 0.75–2.85) and for blood cadmium was 2.88 (95% CI of 1.10–7.50). Another study found a modest increase in systolic or diastolic blood pressure associated with increasing blood cadmium levels (geometric mean blood cadmium levels among all participants was 0.4 µg/L); no associations with blood pressure and urinary cadmium levels were found (Tellez-Plaza et al. 2008). The association between blood cadmium levels and blood pressure was stronger in participants who never smoked than in former smokers or current smokers. There were no associations between hypertension and cadmium levels in blood or urine. In the third study, analysis on 4,912 participants (45–79 years old) in the NHANES 1988–1994 survey found a significant association between urinary cadmium levels and myocardial infarction in women, but not men (Everett and Frithsen 2008). After adjusting for numerous risk factors including smoking, race, and family history, a significant increase in the risk of myocardial infarction was observed in women with urinary cadmium levels of ≥ 0.88 µg/g creatinine. Agarwal et al. (2011) found significantly higher blood cadmium levels among participants with cardiovascular and cerebrovascular disease in the NHANES 1999–2006 survey, as compared to participants without disease. The odds ratio of cardiovascular and cerebrovascular disease comparing the lowest blood cadmium quartile to the highest quartile was 1.44 (95% CI of 1.07–1.95) after adjusting for age, gender, race, education, hypertension, diabetes, hypercholesterolemia, BMI, c-reactive protein, and smoking. Peters et al. (2010) found that a 50% increase in blood or urinary cadmium levels resulted in a significant increase in the risk of stroke and congestive heart failure among participants in the NHANES survey. After adjusting for age, gender, race/ethnicity, education, BMI, poverty income ratio, alcohol consumption, smoking status, and disease (diabetes, hypertension, hypercholesterolemia, and chronic kidney disease), the odds ratios (95% CI) for stroke were 1.38 (1.14–1.67) and 1.10 (1.00–1.20) for 50% increases in blood and urinary cadmium levels, respectively; 50% increases in blood and urinary cadmium levels resulted in odds ratios (95% CI) for congestive heart failure of 1.48 (1.17–1.87) and 1.12 (1.04–1.21), respectively. A significant negative correlation between urinary cadmium levels and volume of oxygen consumed at sub-maximum activity (VO₂ max) among white males or Mexican American females (Egwuogu et al. 2009); however, no significant associations were found in black or Mexican American males and white and black females. Using a similar approach, Eum et al. (2008) and Lee et al. (2011) used data from the

3. HEALTH EFFECTS

Korean National Health and Nutrition Examination Survey (KNHANES) to assess the possible associations between cadmium exposure and cardiovascular effects. Eum et al. (2008) found a positive association (adjusted for age, gender, education, smoking status, alcohol intake, BMI, self-reported hypertension, family history of hypertension, and blood lead level) between blood cadmium levels and systolic, diastolic, and mean arterial blood pressure among adults. When comparing participants with the highest tertile of blood cadmium (1.87–5.52 µg/L) to those in the lowest tertile (0.18–1.28 µg/L), the multivariable adjusted odds ratio was 1.521 (95% CI of 1.129–2.049). In a similar analysis, Lee et al. (2011) divided the subjects by gender and found that an interquartile range increase (0.91 µg/L) in blood cadmium was associated with an elevated risk of hypertension (odds ratio of 1.4; 95% CI of 1.1–1.8) only in men. Lee et al. (2011) also found significant associations between an interquartile range increase in blood cadmium and the risk of ischemic heart disease in women (odds ratio of 2.28; 95% CI of 1.26–4.15). No significant associations between blood cadmium and risk of stroke were found.

In a study of children enrolled in the Treatment of Lead-Exposed Children trial, no significant associations between blood cadmium levels and blood pressure in 5 and 7 years olds following treatment for elevated blood lead levels (Cao et al. 2009).

A single gavage dose of 150 mg/kg cadmium in male Sprague-Dawley rats had no effect on blood pressure (Kotsonis and Klaassen 1977). Oral exposure of rats, rabbits, and monkeys to cadmium over intermediate and chronic durations has been found to increase blood pressure in some studies (Akahori et al. 1994; Boscolo and Carmignani 1986; Carmignani and Boscolo 1984; Kopp et al. 1982; Perry et al. 1989; Tomera and Harakal 1988), but not in others (Fingerle et al. 1982; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Mangler et al. 1988; Wills et al. 1981). In general, studies showing an effect on blood pressure have had control groups with lower blood pressure than studies showing no effect, and observed increases in blood pressure are generally small. At least in rats, the effect on blood pressure appears to be biphasic, reaching a maximum effect (an increase of 12–14 mm Hg in average systolic pressure) at intakes of 0.07 mg/kg/day, but decreasing to normal or even below normal at intakes 10–100 times higher (Kopp et al. 1982). Enlarged and arteriosclerotic hearts have been found in rats orally exposed to 0.35 mg Cd/kg/day for 3 years (Schroeder et al. 1965) or to 2.79 mg Cd/kg/day for 100 days (Wilson et al. 1941), but this effect is likely to be secondary to cadmium-induced anemia (Wilson et al. 1941). Histopathologic lesions of heart tissues (congestion, separation of muscle fibers) and decreased activity of antioxidant enzymes, but no increase in peroxidation, were found among rats given 2.5 mg/kg/day of cadmium in the diet for 7 weeks (Jamall et al. 1989).

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Gastrointestinal Effects. Numerous human and animal studies indicate that oral exposure to cadmium in high concentrations causes severe irritation to the gastrointestinal epithelium (Andersen et al. 1988; Frant and Kleeman 1941). Common symptoms in humans following ingestion of food or beverages containing high concentrations of cadmium include nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although exact doses have not been measured, gastrointestinal symptoms have been caused in children by 16 mg/L cadmium in soft drinks (Nordberg et al. 1973) and 13 mg/L cadmium in popsicles (Frant and Kleeman 1941). Assuming an intake of 0.15 L (Nordberg et al. 1973) and a body weight of 35 kg, the emetic dose is 0.07 mg/kg. Although few studies have specifically examined gastrointestinal effects of longer-term cadmium exposure, no surveys of environmentally exposed populations have reported gastrointestinal symptoms (Morgan and Simms 1988; Roels et al. 1981a; Shigematsu 1984).

In rats and mice, histopathologic lesions (e.g., severe necrosis, hemorrhage, ulcers) in the gastrointestinal epithelium have been observed after high (>30 mg/kg/day) acute-duration oral cadmium exposure by gavage (Andersen et al. 1988; Basinger et al. 1988; Machemer and Lorke 1981), but not after lower levels (8 mg/kg/day in drinking water) for 24 weeks (Kotsonis and Klaassen 1978).

Hematological Effects. Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. Anemia has been found in some instances among humans with chronic dietary exposure to cadmium (Kagamimori et al. 1986), but other studies have found no significant relationship between dietary cadmium exposure and anemia in humans (Roels et al. 1981a; Shiwen et al. 1990). Hypoproteinemia and hypoalbuminemia were reported in a male who ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

A number of studies have demonstrated that oral exposure to cadmium frequently produces anemia in laboratory animals, and that additional iron prevents anemia (Decker et al. 1958; Groten et al. 1990; Hays and Margaretten 1985; Itokawa et al. 1974; Kawamura et al. 1978; Kelman et al. 1978; Kozłowska et al. 1993; Ogoshi et al. 1989; Pleasants et al. 1992, 1993; Pond and Walker 1972; Sakata et al. 1988; Sorell and Graziano 1990; Stowe et al. 1972; Watanabe et al. 1986; Webster 1978; Wilson et al. 1941). Decreases in serum iron have also been reported (Prigge 1978a). Borzelleca et al. (1989) reported slight but statistically significant increases in hemoglobin, hematocrit, and erythrocytes in male rats at 65.6 mg/kg/day once a day for 10 days, but no change in females. Male Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium showed no signs of anemia 14 days later (Kotsonis and

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Klaassen 1977), but anemia was produced in male Wistar rats after 12 days of drinking-water exposure to 12 mg/kg/day (Sakata et al. 1988). Most intermediate-duration exposure studies in rats have shown evidence of anemia at doses of 2–14 mg/kg day (Decker et al. 1958; Groten et al. 1990; Itokawa et al. 1974; Kawamura et al. 1978; Pleasants et al. 1993; Pond and Walker 1972; Sakata et al. 1988; Wilson et al. 1941). However, some intermediate-duration studies have found no change in hemoglobin (Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Petering et al. 1979; Prigge 1978a) in rats treated at similar doses. Anemia has also been seen in intermediate-duration studies in mice (Webster 1978) and rabbits (Stowe et al. 1972), but not in dogs (Loeser and Lorke 1977b). The result in dogs may be due to the relatively low dose of cadmium (0.75 mg/kg/day) used in this study. Hematological effects following chronic-duration oral exposure to cadmium are less well characterized. In monkeys maintained on 4 mg/kg/day cadmium in food, pale feces, and clinical signs of anemia occurred after 90 weeks, but the anemia was associated with a decreased food intake rather than an increase in reticulocytes (Masaoka et al. 1994). Anemia was not present in rats exposed via drinking water for 12 months to the relatively low dose of 0.79 mg/kg/day (Decker et al. 1958). The number of erythroid progenitor cells in bone marrow is decreased in mice exposed to 57 mg/kg/day of cadmium in drinking water for 12 months (Hays and Margaretten 1985), but is increased in rats exposed to 12 mg/kg/day of cadmium in drinking water for up to 100 days (Sakata et al. 1988). Thus, the question remains open whether factors, in addition to reduced gastrointestinal absorption of iron, such as direct cytotoxicity to marrow or inhibition of heme synthesis may contribute to anemia.

Musculoskeletal Effects. Osteomalacia, osteoporosis, bone fractures, and decreased bone mineral density have been observed in several populations exposed to elevated levels of cadmium in the diet. Bone effects were first reported in residents in the Jinzu River Basin, a cadmium-contaminated area in Japan. The disease termed Itai-Itai or "ouch-ouch" disease most often affected women with several risk factors such as poor nutrition, multiparity, and postmenopausal status (Shigematsu 1984). The disease was characterized by multiple fractures of the long bones, osteomalacia, and osteoporosis in combination with proteinuria (Järup et al. 1998b; Nordberg et al. 1997). Other Japanese populations with dietary cadmium exposure have also been found to have elevated osteoporosis and osteomalacia in both men and women (Kido et al. 1989b). Kagamimori et al. (1986) evaluated elderly Japanese women with heavy cadmium exposure from ingesting polluted drinking water, rice, and fish during World Wars I and II; and continued low-grade cadmium exposure from agricultural produce. Of 56 cases of Itai-Itai disease, 26 were accompanied by osteomalacia and 26 were without osteomalacia. Another study found that the degree of loss of bone density is correlated with urinary excretion of β_2 -microglobulin, an index of renal injury (see Section 3.5.2) (Kido et al. 1990a). The bone effects observed in Itai-Itai disease and in other

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studies of Japanese populations exposed to high levels of cadmium in rice are primarily due to kidney damage, which results from a progressive disturbance in renal metabolism of vitamin D to its biologically active form (Nogawa et al. 1987, 1990) and an increased urinary excretion of calcium (Buchet et al. 1990). These results suggest that bone changes may be secondary to disruption in kidney of vitamin D metabolism and resulting imbalances in calcium absorption and excretion. A recent study of women living in the Jinzu River basin found that bone turnover, particularly bone formation, was influenced by renal tubular function (Aoshima et al. 2003). However, it is possible that some bone effects are not mediated via the kidney.

Bone effects have also been observed in communities outside of Japan and in populations exposed to low levels of cadmium. In a study of Swedish women environmentally exposed to cadmium, a significant negative relationship between urinary cadmium levels and bone mineral density was observed (Åkesson et al. 2005); the mean urinary cadmium level of the population was 0.52 µg/L. In Swedish residents living in an area with known cadmium pollution from battery manufacturing facilities, significant associations were noted between blood cadmium levels and bone mineral density and between urinary cadmium levels and risk of fractures and osteoporosis. There were significant decreases in bone mineral density in environmentally exposed subjects older than 60 years of age with blood cadmium levels of ≥ 0.56 µg/L (Alfvén et al. 2002a). Increases in the risk of bone fractures were observed in subjects (approximately 10% of all subjects examined had environmental and occupational exposure to cadmium) older than 50 years of age with urinary cadmium levels >2 µg/g creatinine; no significant associations were found in subjects under 50 years of age (Alfvén et al. 2004). Another study of this population found significant increases in the risk of osteoporosis among men >60 years of age with urinary cadmium levels ≥ 5 µg/g creatinine; however, an increased risk of osteoporosis was not observed in women (Alfvén et al. 2000). A Belgian study in which residents living near zinc smelters found a 2-fold increase in cadmium exposure (as assessed via urinary cadmium levels) was associated with a decrease in proximal and distal forearm bone density of approximately 0.1 g/cm² among postmenopausal women (Staessen et al. 1999). For women with urinary cadmium levels >1 µg/day, the incidence of bone fracture was 13.5 per 1,000 person-years. Another study of a subset of the women living near a zinc smelters (Schutte et al. 2008) provides suggestive evidence that cadmium has a direct osteotoxic effect. Significant associations between urinary cadmium levels and the levels of two pyridinium crosslinks of collagen (urinary levels of hydroxylsypyridinoline and lysypyridinoline), proximal forearm bone mineral density, and serum parathyroid hormone levels were found. In almost all of the examined women, urinary levels of retinol binding protein were below the cut-off level of 338 µg/day, suggesting no cadmium-induced effect on renal tubular function. Several biomarkers of bone damage were examined in a subsequent follow-up

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study of some of the women (Schutte et al. 2008) only 1 of the 294 women examined had evidence of renal dysfunction (increased retinol binding protein). Significant associations between urinary cadmium excretion and two biomarkers of bone resorption (urinary hydroxyllysylpyridinoline and lysylpyridinoline) were found. Although significant associations between urinary cadmium levels and biomarkers of renal dysfunction were observed in Polish adults living in a cadmium-polluted area, the only association between urinary cadmium and bone biomarkers was a significant decrease in bone mineral density among males with urinary cadmium levels of $\geq 2 \mu\text{g/g}$ creatinine (Trzcinka-Ochocka et al. 2010). Similar results have been observed in several studies of residents living in areas of China with moderate or high cadmium pollution levels (Jin et al. 2004b; Nordberg et al. 2002; Wang et al. 2003; Zhu et al. 2004). There were significant increases in the prevalence of low forearm bone mineral density in postmenopausal women with urinary cadmium levels $>20 \mu\text{g/g}$ creatinine and in men, premenopausal women, and postmenopausal women with blood cadmium levels $>20 \mu\text{g/L}$ (Nordberg et al. 2002). An increase in bone fractures was observed in males and females over the age of 40 years living in the area of high cadmium exposure (mean urinary cadmium levels in the area were 9.20 and 12.86 $\mu\text{g/g}$ creatinine in the males and females, respectively) (Wang et al. 2003). A significant dose-response relationship between urinary cadmium levels and the prevalence of osteoporosis was observed (Jin et al. 2004b; Wang et al. 2003; Zhu et al. 2004); the Jin et al. (2004b) study found that 23 of the 31 subjects with osteoporosis also exhibited signs of renal dysfunction. A subsequent study by this group examined 316 male and female residents living in areas with moderate or heavy cadmium pollution 10 years after the source of rice was switched to commercially available rice from nonpolluted areas (Chen et al. 2009). As in the earlier studies, significant decreases in forearm bone mineral density were observed in the women living in the moderately polluted area and in the men and women living in the heavily polluted areas. When the subjects were divided by age, decreases in bone mineral density were observed in women 60–69 or ≥ 70 years old in both cadmium polluted areas and in men ≥ 70 years living in the heavily polluted area. A significantly higher prevalence of osteoporosis was also observed in women living in the polluted areas and the prevalence increased with increasing urinary cadmium levels. In another study of this population, Chen et al. (2011) found a higher prevalence of osteoporosis (assessed in 2006) among women with renal dysfunction (urinary albumin $>15 \text{ mg/g}$ creatinine and urinary NAG $\geq 12 \text{ IU/g}$ creatinine; renal biomarkers assessed in 1998) or tubular damage (urinary NAG $\geq 12 \text{ IU/g}$ creatinine); no significant association was found for glomerular damage (urinary albumin $\geq 15 \text{ mg/g}$ creatinine). Significantly lower bone mineral density levels were also found in women with tubular damage, as compared to those without tubular damage. In men, no significant associations between the prevalence of osteoporosis or bone mineral density and alterations in renal biomarkers were found. Chen et al. (2011) also compared the change in bone mineral damage from 1998 to 2006 in subjects with and without evidence of kidney

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damage and found a significantly greater decrease in bone mineral damage among women with tubular damage. In a study of adults living near an industrial complex in Korea, significant associations between high urinary cadmium levels ($\geq 1.0 \mu\text{g/g}$ creatinine) and osteopenia were observed in males and females (Shin et al. 2011). Bone mineral density was also negatively associated with urinary cadmium levels.

In a substudy of a population-based health survey in Sweden (Engström et al. 2009), a significantly lower bone mineral density was observed in postmenopausal women with elevated urinary cadmium levels (median of $1.1 \mu\text{g/g}$ creatinine, 5–95th percentile of $0.69\text{--}1.7 \mu\text{g/g}$ creatinine) as compared to women with low urinary cadmium levels (median of $0.36 \mu\text{g/g}$ creatinine; 5–95th percentile of $0.18\text{--}0.73 \mu\text{g/g}$ creatinine). Significant decreases in serum parathyroid hormone levels and increases in urinary deoxypyridinoline levels (indicative of increased bone resorption) were also found in the high urinary cadmium group; however, there were no significant alterations in serum 1,25-dihydroxyvitamin D levels. Significant elevations in biomarkers of renal dysfunction (urinary NAG and pHG and estimated glomerular filtration rate) were also in the high urinary cadmium group. In the U.S. general population (using data collected during NHANES III, 1988–1994), a significant association was found between urinary cadmium levels and osteopenia and osteoporosis among adults with urinary cadmium levels of $>1 \mu\text{g/g}$ creatinine (Wu et al. 2010). Using the same NHANES data set, Gallagher et al. (2008) found a 43% increased risk of osteoporosis (hip bone mineral density defined) (odds ratio of 1.43; 95% CI of 1.02–2.00) among women ≥ 50 years of age with urinary cadmium levels of $0.50\text{--}1.00 \mu\text{g/g}$ creatinine, as compared to women with urinary cadmium levels of $<0.50 \mu\text{g/g}$ creatinine.

Using data collected during NHANES III (1988–1994), Arora et al. (2008, 2008) examined the possible association between urinary cadmium levels and dental health in children and adults. In children aged 6–12 years, a significant association (adjusted for age, gender, ethnicity, education level, poverty status, log-transformed blood lead, log-transformed serum cotinine, and dietary sucrose intake) between urinary cadmium levels and dental caries in deciduous teeth among children with low external tobacco smoke exposure; no significant associations were found in permanent teeth (Arora et al. 2008). A significant association (after adjustment for gender, age, education level of household head, race/ethnicity, household poverty status, time since last visit to dentist, missing teeth, serum cotinine, smoking habits, exposure to external tobacco smoke, blood lead, diabetes, renal dysfunction, and bone mineral density) between urinary cadmium and periodontal disease (presence of attachment loss of at least 4 mm in $>10\%$ of sites examined) in adults (≥ 18 years of age) (Arora et al. 2009). A logistic regression model predicted a 56% increase in the prevalence of periodontal disease associated with a 3-fold increase in urinary cadmium levels ($0.18\text{--}0.63 \mu\text{g/g}$ creatinine).

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A number of animal studies confirm the findings of the epidemiology data suggesting that the bone is a sensitive target of cadmium toxicity. Decreases in bone mineralization and bone mineral density have been observed in female rats exposed to ≥ 0.2 mg Cd/kg/day in the lumbar spine, femur, and tibia (Brzóska et al. 2004b, 2005a, 2005b, 2005c) and in male rats exposed to ≥ 0.5 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b; Brzóska et al. 2010; Yokota and Tonami 2008) for an intermediate duration and in female rats chronically exposed to 0.08 mg Cd/kg/day (Brzóska 2012; Brzóska and Moniuszko-Jakoniuk 2004a, 2004b). In the series of studies conducted by Brzóska and associates, the occurrence of osteopenia and osteoporosis was evaluated using data for bone mineral density of the cadmium-exposed rats, control rats, and healthy adult rats. Osteopenia was observed in male rats exposed to 0.5 mg Cd/kg/day for 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) and in female rats exposed to 0.08 mg Cd/kg/day for 12 or 18 months (Brzóska and Moniuszko-Jakoniuk 2004a, 2004b); osteoporosis was observed in male rats exposed to 4 mg Cd/kg/day for 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) and in female rats exposed to 0.08 mg Cd/kg/day for 24 months (Brzóska and Moniuszko-Jakoniuk 2004a, 2004b).

The decreases in bone mineralization resulted in altered mechanical properties (e.g., stiffness, load, displacement at load) of the vertebral body, femur, and tibia and increases in the number of animals with deformed or fractured lumbar spinal bone in female rats exposed to ≥ 0.2 mg Cd/kg/day for an intermediate duration (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005b, 2005a, 2005c, 2010; Ogoshi et al. 1989); increases in lumbar spine deformities were also observed in male rats exposed to 0.5 mg Cd/kg/day for 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b) and in female rats exposed to 0.08 mg Cd/kg/day for 24 months (Brzóska 2012; Brzóska and Moniuszko-Jakoniuk 2004a, 2004b).

The studies by Brzóska and associates reported significant alterations in biochemical markers of bone turnover. During the first 6 months of a 1-year study, significant decreases in osteocalcin concentrations were observed in female rats exposed to ≥ 0.2 mg Cd/kg/day; no alterations were observed during the last 6 months of the study (Brzóska and Moniuszko-Jakoniuk 2005d). Observed changes in alkaline phosphatase levels included decreases in total serum levels in the 4 mg Cd/kg/day group after 6, 9, or 12 months of exposure, decreases in trabecular bone levels at ≥ 0.2 mg Cd/kg/day after 3, 6, or 9 months of exposure and at 0.5 mg Cd/kg/day at 12 months, decreases in cortical bone levels at 4 mg Cd/kg/day after 3 months of exposure, and increases in trabecular bone and cortical bone alkaline phosphatase at 4 mg Cd/kg/day after 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). Serum C-terminal

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telopeptides of type I collagen concentration (CTX) was significantly decreased after 3 or 6 months of exposure or increased after 9 or 12 months in rats exposed to ≥ 0.2 mg Cd/kg/day (Brzóška and Moniuszko-Jakoniuk 2005d). As noted by Brzóška and Moniuszko-Jakoniuk (2005d), these alterations in bone turnover markers indicate that cadmium exposure at the stage of intensive skeletal development leads to low bone turnover and induces high bone turnover due to enhanced resorption at the stage of consolidation of bone mass and at skeletal maturity.

Decreased calcium content of bone and increased urinary calcium excretion are common findings in intermediate- and chronic-duration studies in the 0.2–8 mg Cd/kg/day range (Brzóška and Moniuszko-Jakoniuk 2005d; Kawamura et al. 1978; Nogawa et al. 1981b; Pleasants et al. 1992; Watanabe et al. 1986). In contrast, Kotsonis and Klaassen (1978) reported no change in bone calcification after a 24-week exposure via drinking water at 8 mg/kg/day, and Kelman et al. (1978) reported no significant change in stable or radiolabeled calcium in any maternal rat tissues from a 3.8 mg/kg/day in drinking water for 22 days during gestation.

Gender, age, and nutritional state appear to influence cadmium toxicity on bone. In the series of experiments conducted by Brzóška and associates, alterations in bone mineral density and the mechanical strength of the lumbar spine and femur were observed in female rats exposed to ≥ 0.2 mg Cd/kg/day and in male rats at 0.5 mg Cd/kg/day (Brzóška and Moniuszko-Jakoniuk 2005a, 2005b, 2005d; Brzoska et al. 2005a, 2005c); no adverse bone effects were observed in males exposed to 0.2 mg Cd/kg/day. In the Ogoshi et al. (1989) study, decreases in the mechanical strength of the femur bone were observed in young rats (21 days of age) exposed to 0.8 mg Cd/kg/day for 4 weeks; however, no alterations in bone strength were observed in adult (24 weeks of age) or elderly (1.5 years of age) rats exposed to cadmium doses as high as 25.6 mg Cd/kg/day for 4 weeks. Adverse effects on bone are exacerbated by a calcium-deficient diet (Itokawa et al. 1974; Kimura et al. 1974; Larsson and Piscator 1971; Wang and Bhattacharyya 1993; Wang et al. 1994), by ovariectomy (Bhattacharyya et al. 1988c), or by multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b).

Hepatic Effects. Liver damage is not usually associated with oral cadmium exposure, except at very high levels of exposure. In humans, a fatal dose of cadmium can cause pronounced liver damage (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). Nishino et al. (1988) reported increased serum concentrations of the urea-cycle amino acids among individuals exposed to cadmium in the diet, and that these levels reflected liver as well as kidney damage. No cadmium-related alterations in liver biomarkers including serum levels of alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase,

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lactate dehydrogenase, and γ -glutamyl transpeptidase were observed in women living in cadmium nonpolluted areas in Japan (Ikeda et al. 1997, 2000). No other studies were located regarding hepatic effects in humans after oral exposure to cadmium.

Hepatic effects have been found in rats, mice, and rabbits after oral cadmium exposure. Acute exposure via gavage at doses of 30–138 mg/kg/day causes liver necrosis in most studies (Andersen et al. 1988; Basinger et al. 1988; Borzelleca et al. 1989; Shimizu and Morita 1990), although histopathologic evidence of liver damage was not seen in one study at a gavage dose of 150 mg/kg (Kotsonis and Klaassen 1977). Exposure of rats for 10 days to drinking water containing 13.9 mg Cd/kg/day was without effect on the liver (Borzelleca et al. 1989). Depletion of liver glutathione by fasting increases the liver necrosis following acute oral exposure to cadmium in rats (Shimizu and Morita 1990).

In a 10-week study, male Rhesus monkeys exposed to 4 mg/kg/day cadmium chloride via gavage, had a significant decrease in glutathione peroxidase in liver, kidney, heart, and lung in the following order: liver>kidney>heart>lung; a significant decrease in glutathione *S*-transferase (GST) activity towards 1-chloro-2,4-dinitrobenzene in all four organs in the following order: liver>lung>kidney>heart; and a significant increase in GST activity towards ethacrynic acid in all four organs in the following order: heart>lung>kidney>liver (Sidhu et al. 1993). Intermediate-duration exposure causes histopathologic changes in the liver (e.g., necrosis of central lobules, focal hepatic fibrosis, biliary hyperplasia) at doses of 1.6–15 mg/kg/day (Cha 1987; Gill et al. 1989b; Miller et al. 1974a; Renugadevi and Prabu 2010; Schroeder et al. 1965; Stowe et al. 1972; Wilson et al. 1941), and metabolic alterations (e.g., decreased cytochrome c oxidase activity in mitochondria, increased ALT and AST activities) at doses of 0.05–10 mg/kg/day (Groten et al. 1990; Muller and Stacey 1988; Muller et al. 1988; Renugadevi and Prabu 2010; Sporn et al. 1970; Steibert et al. 1984; Tewari et al. 1986b). Decreased relative liver weight to body weight has also been reported in male rats fed 5.95 mg/kg/day for 6 weeks (Kozłowska et al. 1993).

Hypertriglyceridemia was observed in male rats exposed to 18 mg Cd/kg/day as cadmium chloride in the drinking water for 8 weeks (Larregle et al. 2008); the increase in plasma triglycerides was likely due to a decrease in lipoprotein lipase activity (key enzyme in triglyceride hydrolysis). A significant increase in liver triglyceride level was also observed; this increase was attributed to increased triglyceride synthesis.

Other intermediate and chronic duration studies have not found liver effects in animals following oral exposure. These studies include a daily gavage exposure of 14 mg/kg/day for 6 weeks in rats (Hopf et al. 1990), a 3-month exposure to cadmium in food at 3 mg/kg/day in rats (Loeser and Lorke 1977a), a

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24-week exposure to cadmium in water at 8 mg/kg/day in rats (Kotsonis and Klaassen 1978), and a 3-month exposure in food at 0.75 mg/kg/day in dogs (Loeser and Lorke 1977b). Kopp et al. (1982) report no hepatic effects from a chronic exposure of 18 months to cadmium in water at 0.65 mg/kg/day in rats.

Renal Effects. Numerous studies indicate that the kidney is the primary target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure (see Section 3.2.1.2). Most of the data involves chronic exposure to cadmium; two case reports involving acute exposure to large doses of cadmium also found kidney effects. In two fatal cases of oral cadmium poisoning, anuria was present in one individual who ingested 25 mg/kg cadmium as cadmium iodide. Damage to the kidneys was reported at autopsy, but was not further specified (Wisniewska-Knypl et al. 1971). The kidneys were reported as normal at autopsy in an individual who died 2 days after ingesting 1,840 mg/kg cadmium (Buckler et al. 1986).

Several studies have found associations between increased mortality and renal dysfunction in residents living in cadmium polluted areas. Significant increases in SMRs were found in residents living in cadmium polluted areas of Japan with elevated levels of biomarkers of renal dysfunction (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006). Among the studies that examined cause of death, significant increases in deaths from renal diseases were found in the residents that were categorized as biomarker-positive (urinary levels of the renal biomarker was higher than the cut-off value); the cut-off values used were β 2-microglobulin $\geq 1,000$ μ g/g creatinine (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Nakagawa et al. 1993; Nishijo et al. 2004a, 2006) or retinol binding protein ≥ 4 mg/L (Nishijo et al. 1995). Other studies have found that mortality increased in proportion to the renal biomarker level (β 2-microglobulin, protein, or glucose) (Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 2004a, 2006). Increases in mortality from renal diseases have also been observed among populations living in cadmium polluted areas of Belgium (Lauwerys and De Wals 1981) and England (Inskip et al. 1982); however, statistical analysis was not reported in the Belgium study and the increase in renal disease was not statistically significant in the other study. In a nationwide study in Japan, no significant associations between the levels of cadmium in brown rice and deaths from all causes or age-adjusted renal insufficiency mortality rate were found (Koizumi et al. 2010).

Elevated levels of several biomarkers of renal dysfunction and/or associations between cadmium burden and these biomarkers have been found in studies of populations living in cadmium nonpolluted areas of Japan (Ezaki et al. 2003; Ikeda et al. 1999; Suwazono et al. 2000; Oo et al. 2000; Uno et al. 2005;

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Yamanaka et al. 1998), South Korea (Hwangbo et al. 2011), Belgium (Buchet et al. 1990; Roels et al. 1981a), and the United States (Ferraro et al. 2010; Noonan et al. 2002) and in populations living in cadmium polluted areas of China (Cai et al. 1990, 1992, 1998; Jin et al. 2002, 2004a, 2004c; Nordberg et al. 1997; Wu et al. 2001), Japan (Cai et al. 2001; Hayano et al. 1996; Horiguchi et al. 2010; Ishizaki et al. 1989; Izuno et al. 2000; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002b, 2009b; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Osawa et al. 2001; Watanabe et al. 2002), Thailand (Honda et al. 2010; Teeyakasem et al. 2007), Sri Lanka (Bandara et al. 2010), Sweden (Järup et al. 2000; Olsson et al. 2002), and Poland (Trzcinka-Ochocka et al. 2004). Most of these studies did not estimate cadmium intake; rather, exposure was characterized based on the levels of cadmium in rice, blood, or urine. The oral route is assumed to be the primary route of exposure, although the inhalation route, particularly in smokers, may have contributed to the overall cadmium body burden. The epidemiology data are summarized in [Table 3-7](#) and brief discussions of the better designed studies providing valuable dose-response data follows.

Buchet et al. (1990) examined 1,699 non-occupationally exposed males and females (aged 20–80 years) living in Belgium. Urinary cadmium levels significantly correlated with urinary β 2-microglobulin, retinol binding protein, NAG, amino acid, and calcium levels; the partial r^2 values were 0.0036, 0.0210, 0.0684, 0.0160, and 0.0168, respectively. The probability that individuals would have abnormal values for the renal biomarkers (defined as >95th percentile for subjects without diabetes or urinary tract diseases and who did not regularly take analgesics) was estimated using logistic regression models with adjustments for age, gender, smoking, disease, and use of analgesics. It was estimated that >10% of β 2-microglobulin, retinol binding protein, amino acid, and calcium values would be abnormal when 24-hour urinary cadmium levels were >3.05, 2.87, 2.74, 4.29, or 1.92 μ g/24 hour, respectively.

Järup et al. (2000) examined 1,021 individuals living near a nickel-cadmium battery plant in Sweden for at least 5 years (n=799) or employed as battery workers (n=222). The mean urinary cadmium levels were 0.81 and 0.65 μ g/g creatinine in males and females, respectively. Urinary cadmium levels were significantly associated with urinary human complex-forming glycoprotein (pHC; also referred to as α 1-microglobulin) levels, after adjustment for age. The relationship remained statistically significant after removal of the cadmium workers from the analysis. The prevalence of abnormal pHC values (defined as exceeding the 95th percentile in a Swedish reference population; >7.1 and 5.3 mg/g creatinine for males and females, respectively) was estimated to increase by 10% at urinary cadmium levels of 1 μ g/g creatinine. The European Chemicals Bureau (2007) recalculated the probability of HC proteinuria (using the raw data from Järup and associates) to account for the differences in age of the reference

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Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
General population (Japan) 10,753 females; 35–60 years old	1.26 µg/g creat.	β2M pHC	Significant correlation between urinary cadmium and effect biomarkers; however, no significant relationship was established when age was factored into analysis.	Ezaki et al. 2003
General population (Japan) 470 nonsmoking females	2.1 µg/g creat.	β2M pHC	Significant correlation between urinary cadmium (not corrected for creat.) and pHC and β2M.	Ikeda et al. 1999
General population (Japan) 1,105 males, 1,648 females; >50 years old	1.8 µg/g creat. (M) 2.4 µg/g creat. (F)	β2M Total protein NAG	Significant correlation between urinary cadmium and protein and β2M. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Suwazono et al. 2000
General population (Japan) 568 males, 742 females; ≥50 years old	2.2–3.4 µg/L (M) 2.8–3.9 µg/L (F)	total protein NAG β2M	Significant correlation (with age adjustment) between urinary cadmium and effect biomarkers.	Oo et al. 2000
General population (Japan) 558 males, 743 females; ≥50 years old	1.3 µg/g creat. (M) 1.3 µg/g creat. (F)	β2M total protein NAG	Significant correlation between urinary cadmium and effect biomarkers (NAG was only significant in females). Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Yamanaka et al. 1998
General population (Japan) 410 males, 418 females; 40–59 years old	0.8 µg/g creat. (M) 1.8 µg/g creat. (F) (median levels)	β2M protein NAG	Significant associations between urinary cadmium and effect biomarkers (protein only significant in males). Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Uno et al. 2005
General population (South Korea) 955 males, 954 females; ≥20 years of age		Glomerular filtration rate	Significant association between elevated blood cadmium levels and decreased glomerular filtration rate in females only.	Hwangbo et al. 2011

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Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
General population (Belgium) 175 females; mean age 81.1–82.3 years old	0.040–0.093 µg/hour	β2M protein amino acids albumin	Dose-response relationship between urinary cadmium and urinary protein and amino acids; significant relationship with β2M and albumin only in the two areas with highest urinary cadmium levels.	Roels et al. 1981a
General population (Belgium) 1,699 males, females; 20–80 years old		β2M protein NAG amino acids calcium	Significant correlation between urinary cadmium and effect biomarkers. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Buchet et al. 1990
General population (United States) 88 males, 71 females; 6–17 years old; 71 males, 80 females; ≥18 years old	0.07 µg/g creat. (M, child) 0.08 µg/g creat. (F, child) 0.24 µg/g creat. (M, adult) 0.23 µg/g creat. (F, adult)	β2M NAG AAP albumin	No significant associations (after correction for age, sex) between urinary cadmium and effect biomarkers in children. Significant association (after age and gender adjustment) between urinary cadmium and NAG and AAP in adults. Dose-response relationship between urinary cadmium and NAG and AAP.	Noonan et al. 2002
General population (United States) 2,644 males, 2,782 females ≥20 years old (data from NHANES 1999–2006)	0.29 µg/g creat.	albumin	Significant association (after age, gender, race/ethnicity, and BMI adjustment) between urinary cadmium >1 µg/g creatinine and urinary albumin to creatinine ratio of >20 mg/g (males) or 30 mg/g (females).	Ferraro et al. 2010
Residents in cadmium-polluted area (China) 433 males and females	11.27 µg/g creat.	β2M NAG	Significantly higher effect biomarkers levels.	Cai et al. 1990, 1992
Residents in cadmium-polluted area (China) 219 males and females		β2M	Significant dose-response relationship between urinary cadmium, blood cadmium, and cumulative Cd intake and β2M; prevalence of abnormal values.	Cai et al. 1998

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Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (China) 118 males, 170 females in high exposure group 80 males, 158 females in moderate exposure group	High: 11.18 µg/g creat. Mod.: 3.55 µg/g creat.	β2M RBP albumin	Significant correlation between urinary cadmium and effect biomarkers. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Jin et al. 2002
Residents in cadmium-polluted area (China) 118 males, 170 females in high exposure group 80 males, 158 females in moderate exposure group		β2M NAG NAG-B RBP albumin	Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Jin et al. 2004c
Residents in cadmium-polluted area (China) 66 males, 22 females	9.12 µg/g creat.	β2M NAG albumin	Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Jin et al. 2004a
Residents in cadmium-polluted area (China) 120 males, 127 females in high exposure group 125 males, 122 females in moderate exposure group	High: 9.40 µg/L (M) 12.13 µg/L (F) Mod.: 1.28 µg/L (M) 2.05 µg/L (F)	β2M albumin	Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Nordberg et al. 1997
Residents in cadmium-polluted area (China) 122 males, 125 females	6.1 µg/g creat. (M) 7.5 µg/g creat. (F)	β2M NAG calcium	Effect biomarkers significantly higher than controls. Dose-response relationship between urinary cadmium and effect biomarkers.	Wu et al. 2001
Residents in cadmium-polluted area (Japan) 127 males; mean age 72.1–73.6 years old	6.8–6.9 µg/g creat.	β2M	Higher prevalence of abnormal effect biomarkers compared to controls.	Cai et al. 2001

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Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (Japan) 1,178 females	3.16–4.08 µg/g creat.	β2M	No significant association between urinary cadmium and effect biomarkers.	Horiguchi et al. 2004
Residents in cadmium-polluted area (Japan) 82 males, 56 females		β2M	Significant association between cadmium intake and effect biomarkers in males only.	Izuno et al. 2000
Residents in cadmium-polluted area (Japan) 634 males, 411 females		Protein	Significant association between cadmium intake and increased prevalence of abnormal levels of urinary protein in males.	Kobayashi et al. 2002a; Watanabe et al. 2002
Residents in cadmium-polluted area (Japan) 1,419 males, 1,745 females	4.6 µg/g creat. (M) 7.2 µg/g creat. (F)	Potassium sodium	Significantly higher urinary potassium levels, compared to controls. Significant correlation between urinary potassium and urinary cadmium and β2M. Urinary sodium not significantly different than controls and not correlated with urinary cadmium.	Monzawa et al. 1998
Residents in cadmium-polluted area (Japan) 44 males, 54 females	2.69 µg/g creat. (M) 4.68 µg/g creat. (F)	β2M pHC NAG protein inorganic phosphorus	Significant correlation between urinary cadmium and effect biomarkers (except β2M in males).	Nakadaira and Nishi 2003
Residents in cadmium-polluted area (Japan) 832 males, 871 females		β2M protein amino nitrogen	Significant correlation between cadmium concentration in rice and effect biomarkers. Dose-response relationship between cadmium levels in rice and prevalence of abnormal β2M (males) and protein (females) levels.	Nakashima et al. 1997
Residents in cadmium-polluted area (Japan) 826 males, 641 females		Protein	Dose response relationship between cadmium levels in rice and prevalence of abnormal effect biomarker levels.	Osawa et al. 2001
Residents in cadmium-polluted area (Japan) 878 males, 972 females		β2M	Dose response relationship between cadmium in rice and effect biomarkers.	Nogawa et al. 1989

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Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (Japan) 1,424 males, 1,754 females	4.56 µg/g creat. (M) 7.15 µg/g creat. (F)	β2M	β2M significantly higher than controls. Dose-response relationship between urinary cadmium and prevalence of abnormal β2M levels.	Ishizaki et al. 1989
Residents in cadmium-polluted area (Japan) 878 males, 972 females		β2M	Dose response relationship between cadmium in rice and prevalence of abnormal β2M levels.	Kido and Nogawa 1993
Residents in cadmium-polluted area (Japan) 1,403 males, 1,716 females; ≥50 years old	4.56 µg/g creat. (M) 7.15 µg/g creat. (F)	β2M	Dose response relationship between urinary cadmium and prevalence of abnormal β2M levels.	Hayano et al. 1996
Residents in cadmium-polluted area (Japan) 120 males, 280 females	1.78 µg/g creat. (M) 2.27 µg/g creat. (F)	NAG	Significant correlation between urinary cadmium and NAG.	Kawada et al. 1992
Residents in cadmium-polluted area (Japan) 129 females; 34– 74 years of age	6.30 µg/g creat.	β2M	Significant correlation between urinary cadmium and β2M.	Horiguchi et al. 2010
Residents in cadmium-polluted area (Thailand) 58 males, 70 females	12 µg/g creat.	β2M pHC NAG protein albumin	Significant correlation between urinary cadmium and effect biomarkers. Dose-response relationship between urinary cadmium and prevalence of abnormal β2M levels.	Teeyakasem et al. 2007
Residents in cadmium-polluted area (Thailand) 307 males, 488 females; >30 years of age	5.3 µg/g creat. (M) 5.8 µg/g creat. (F)	β2M NAG	Dose-response relationship between urinary cadmium and prevalence of abnormal β2M levels (≥1,000 µg/g creatinine) in females and NAG (≥9 IU/g creatinine) in males and females.	Honda et al. 2010
Residents in cadmium-polluted area (includes occupationally exposed subjects (Sweden)	0.81 µg/g creat. (M) 0.66 µg/g creat. (F)	pHC	Linear relationship between urinary cadmium and pHC (relationship remained significant after removal of occupationally exposed subjects.	Järup et al. 2000

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Table 3-7. Summary of Human Studies Examining Renal Effects

Population studied	Mean urinary cadmium level	Effect biomarker	Results	Reference
Residents in cadmium-polluted area (Sweden) 57 males, 48 females	0.26 µg/g creat.	β2M protein HC NAG albumin	Significant correlation between urinary and blood cadmium and effect biomarkers. β2M clearance was significantly explained by urinary cadmium levels.	Olsson et al. 2002
Residents in cadmium-polluted area (Poland) 44 males, 128 females only exposed as adults 72 males, 64 females exposed as children	0.97 µg/g creat. (childhood exposure) 2.23 µg/g creat. (adult exposure)	β2M RBP NAG NAG-A NAG-B albumin	In childhood exposure group, significant correlations between urinary cadmium and β2M, RBP, and albumin. In adult exposure group, significant correlations between urinary cadmium and all effect biomarkers.	Trzcinka-Ochocka et al. 2004

AAP = alanine aminopeptidase; β2M = β2-microglobulin; creat. = creatinine; BMI = body mass index; F = female; M = male; Mod. = moderate; NAG = N-acetyl-β-glucosaminidase; NHANES = National Health and Nutrition Examination Survey; pHC = human complex-forming glycoprotein, also referred to as α1M; RBP = retinol binding protein

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population (mean of 40 years) and study population (mean of 53 years). Based on these recalculations, the urinary cadmium level associated with a 10% increased probability of abnormal pH values (20% total probability) was 2.62 $\mu\text{g/g}$ creatinine for the total population. In the environmental exposed subgroup, a urinary cadmium level of 0.5 $\mu\text{g/g}$ creatinine was associated with a 13% probability (doubling of the probability in reference population) of abnormal pH values.

Noonan et al. (2002) examined residents in Pennsylvania living near a defunct zinc smelting facility (geometric mean urinary cadmium level of 0.14 $\mu\text{g/g}$ creatinine) and a reference community located 10 miles from the facility (geometric mean urinary cadmium levels of 0.12 $\mu\text{g/g}$ creatinine). The data from the two communities were pooled because there were no differences in urinary cadmium levels between them. β 2-microglobulin, NAG, alanine aminopeptidase (AAP), and albumin levels were measured as biomarkers of renal dysfunction. The geometric mean urinary cadmium levels were 0.07 and 0.08 $\mu\text{g/g}$ creatinine in 88 males and 71 females aged 6–17 years and 0.24 and 0.23 $\mu\text{g/g}$ creatinine in 71 males and 80 females aged ≥ 18 years. No significant correlations between urinary cadmium levels and renal biomarkers were observed in the children, after adjustment for creatinine, age, and gender. In adults, significant correlations (after adjustment for creatinine, age, gender, smoking, and self-reported diabetes or thyroid disease) between urinary cadmium and NAG (partial correlation coefficient of 0.20, 95% CI of 0.05–0.36) and AAP (partial correlation coefficient of 0.21 and 95% CI of 0.05–0.36) were observed. Significant dose-effect relationships were also found for these two biomarkers. Urinary cadmium levels were not significantly associated with elevated levels of β 2-microglobulin or albumin.

Nogawa et al. (1980) examined 878 males and 972 females aged ≥ 50 years living in the Kakehashi River basin in Japan; the Kakehashi River, cadmium polluted from an upstream mine, was used to irrigate rice fields. β 2-Microglobulin measured in morning urine samples was used as a biomarker of renal dysfunction and cadmium intake was estimated from rice samples collected in 1974. Cadmium levels in rice were considered to be representative of cadmium intake because over 70% of the total cadmium intake has been shown to come from rice. Cadmium in the rice ranged from 0.10 to 0.69 $\mu\text{g/g}$. β 2-Microglobulin levels were significantly higher in the study population compared to a reference population of 113 males and 161 females living in a nearby area. A significant dose-related association between total cadmium intake and prevalence of abnormal β 2-microglobulin values (defined as β 2-microglobulin levels of $\geq 1,000$ $\mu\text{g/g}$ creatinine) was found. The total cadmium intake, which resulted in a prevalence of abnormal β 2-microglobulin levels equal to the control group, was 1,678 mg in males (prevalence in controls was 6.0%) and 1,763 mg in females (prevalence in controls was 5.0%). A further analysis of the exposed subjects (Hochi et al. 1995) found that the prevalence of abnormal

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β 2-microglobulin levels (using a cut-off level of 1,000 μ g/g creatinine) exceeded the prevalence in the reference population when cadmium intake was ≥ 2 g and the subjects were divided into subgroups by age. The prevalence of abnormal β 2-microglobulin levels at a given cadmium intake increased with age.

Yamanaka et al. (1998) examined 558 males and 743 females aged ≥ 50 years living in a cadmium nonpolluted area in Japan. Urinary cadmium level was used as a biomarker of exposure and urinary β 2-microglobulin, total protein, and NAG as biomarkers of renal dysfunction. The geometric mean urinary cadmium levels were 1.3 and 1.3 μ g/g creatinine in males and females, respectively. Significant correlations (after adjustment for age) between urinary cadmium levels and total protein, β 2-microglobulin, and NAG were found. Abnormal levels of renal biomarkers were defined as exceeding the 84% upper limit value calculated from a referent group of 2,778 non-exposed individuals; the cut-off values were 124.8 and 120.8 mg/g creatinine for total protein in males and females, 492 and 403 μ g/g creatinine for β 2-microglobulin, and 8.0 and 8.5 U/g creatinine for NAG. Dose-response relationships between urinary cadmium levels and prevalence of abnormal levels of β 2-microglobulin, total protein, and NAG were found. The odds ratios (95% CI) were 6.589 (3.383–12.833), 3.065 (1.700–5.526), and 1.887 (1.090–3.268) for protein, β 2-microglobulin, and NAG in males and 17.486 (7.520–40.660), 5.625 (3.032–10.435), and 2.313 (1.399–3.824) for protein, β 2-microglobulin, and NAG in females.

Another study of residents living in a cadmium nonpolluted area of Japan examined 346 males and 529 females from one area (area A) and 222 males and 413 females in another area (area B); all subjects were ≥ 50 years of age and were not occupationally exposed to heavy metals (Oo et al. 2000). The geometric mean urinary cadmium levels were 2.2 and 2.8 μ g/L in males and females in area A and 3.4 and 3.9 μ g/L in area B. Significant correlations (with adjustment for age) were found between urinary cadmium and urinary levels of protein, β 2-microglobulin (not significant in males in area B) and NAG levels. A significant association between urinary cadmium levels and the prevalence (cut-off levels from same referent population as Yamanaka et al. 1998) of abnormal levels of urinary protein (cut-off level of 113.8 and 96.8 μ g/L in males and females), β 2-microglobulin (378 and 275 μ g/L) (only significant in females in area A), and NAG (8.0 and 7.2 μ g/L). The odds ratios (95% CI) for an increase in prevalence of abnormal renal biomarkers were 8.810 (3.401–22.819) and 11.282 (3.301–38.362) for protein in males in areas A and B, respectively, 8.234 (3.696–18.343) and 23.901 (8.897–64.210) for protein in females in areas A and B; 2.558 (1.246–5.248) for β 2-microglobulin in females in area A; 47.944 (14.193–161.954) and 9.940 (3.153–31.340) for NAG in males in areas A and B; and 72.945 (21.873–243.263) and 25.374 (9.452–68.117) for NAG in females in areas A and B.

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In a re-examination of the populations studied by Yamanaka et al. (1998) and Oo et al. (2000), Suwazono et al. (2000) measured cadmium levels in blood and urine and urinary levels of total protein, β 2-microglobulin, and NAG in 1,105 males and 1,648 females over the age of 50 years. The geometric mean concentrations of cadmium in urine were 1.8 and 2.4 $\mu\text{g/g}$ creatinine in males and females, respectively, and blood cadmium levels were 2.0 and 1.8 ng/g in males and females. After adjustment for age, significant associations between urinary cadmium levels and urinary protein and β 2-microglobulin in males and females were found. Additionally, blood cadmium levels were significantly associated with urinary protein and NAG levels in males and urinary protein, β 2-microglobulin, and NAG levels in females. Cut-off levels (defined as the 84% upper limit values from 424 male and 1,611 female nonsmoking subjects) of 157.4 and 158.5 mg/g creatinine for protein in males and females, respectively, 507 and 400 $\mu\text{g/g}$ creatinine for β 2-microglobulin in males and females, respectively, and 8.2 and 8.5 $\mu\text{g/g}$ creatinine for NAG in males and females, respectively, were used to evaluate the prevalence of abnormal levels of renal biomarkers. Logistic regression analysis demonstrated significant associations between urinary cadmium levels and increased prevalence of abnormal levels of total protein (odds ratio of 3.923, 95% CI of 2.2028–7.590) and β 2-microglobulin (odds ratio of 2.259, 95% CI of 1.372–3.717) in males; in females, significant associations were found for total protein (odds ratio of 7.763; 95% CI of 4.231–14.243), β 2-microglobulin (odds ratio of 2.259, 95% CI of 1.879–4.281), and NAG (odds ratio of 1.882, 95% CI of 1.311–2.702). For blood cadmium levels, the only significant association found was for an increased prevalence of abnormal total protein levels in females (odds ratio of 3.490, 95% CI of 1.661–7.331).

Jin et al. (2002) examined three populations living various distances from a nonferrous metal smelter. The geometric mean levels of urinary cadmium were 11.18 and 12.86 $\mu\text{g/g}$ creatinine in males ($n=294$) and females ($n=171$) in the highly polluted area, 3.55 and 4.45 $\mu\text{g/g}$ creatinine in males ($n=243$) and females ($n=162$) in the moderately polluted area, and 1.83 and 1.79 $\mu\text{g/g}$ creatinine in males ($n=253$) and females ($n=155$) in the control area. Significant correlations were found between urinary (and blood) cadmium levels and renal biomarkers (β 2-microglobulin, retinol binding protein, and albumin). Cut-off values for β 2-microglobulin, retinol binding protein, and albumin of 300 $\mu\text{g/g}$ creatinine, 300 $\mu\text{g/g}$ creatinine, and 15 mg/g creatinine, respectively, were used to assess possible dose-response relationships (no additional information was provided); although 300 $\mu\text{g/g}$ creatinine was reported as the cut-off values for β 2-microglobulin, subsequent analysis of this data set (Jin et al. 2004c) reported a cut-off value of 800 $\mu\text{g/g}$ creatinine. Significant dose-response relationships between urinary (and blood) cadmium and the prevalence of abnormal levels of renal markers of kidney dysfunction were found.

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Unlike the studies discussed above, Hellström et al. (2001) used the incidence of renal replacement therapy (dialysis or kidney transplantation) as an indicator of renal dysfunction, in particular, end-stage renal disease. Residents of Kalmar County, Sweden were divided into four exposure groups: high exposure (workers at cadmium battery production facility), moderate (residents living within 2 km of the cadmium battery facility), low (residents living between 2 and 10 km of the facility), and no exposure (residents living at least 10 km from the facility); all subjects were 20–79 years of age. The Mantel-Haenszel rate ratio (MH-RR) for renal replacement therapy in the cadmium exposed group was 1.8 (95% CI 1.3–2.3); among the environmentally exposed group, the MH-RR was 1.7 (95% CI 1.3–2.3). The age SRRs were 1.9 (95% CI 1.3–2.5) and 1.9 (95% CI 1.2–2.6) for subjects in the moderate exposure group aged 20–79 years or 40–79 years, respectively. The trend for increasing MH-RR with increasing exposure was statistically significant. The age SRRs were not significantly elevated in the low exposure group. The investigators noted that the causes of end stage renal disease were similar in the cadmium exposed and unexposed groups. When only primary renal diseases (excludes renal failure secondary to diabetes or vascular or systemic diseases) were considered, the MH-RR was 1.7 (95% CI 1.1–2.6) for all cadmium exposed individuals and 2.1 (95% CI 1.4–3.2) for cadmium exposed individuals aged 40–79 years. Although urinary cadmium levels were not assessed in this study, other studies in this area found mean urinary cadmium levels of 1.0 and 0.46 µg/g creatinine in residents living within 0.5 and 0.5–1 km, respectively, of the battery facility (Järup et al. 1995a) and 0.38 and 0.55 µg/g creatinine in men and women, respectively, living in the contaminated area (Alfvén et al. 2000). Ferraro et al. (2011) and Swaddiwudhipong et al. (2011) used another approach for evaluating kidney damage by examining the association between elevated urinary cadmium levels and kidney stone formation. Using the NHANES survey data from 1988 to 1994, Ferraro et al. (2011) found significantly higher urinary cadmium levels in individuals with a history of kidney stone formation, as compared to individuals without a history of kidney stone formation. However, after adjusting for age, race/ethnicity, BMI, smoking habits, region of residence, and daily intake of calcium and sodium, a significant association was only found in females; the odds ratio of kidney stones was 1.40 (95% CI of 1.06–1.86) among individuals with a urinary cadmium level of >1 µg/g. Swaddiwudhipong et al. (2011) found a significant association between urinary cadmium levels and prevalence of urinary stone formation among adults living in cadmium-contaminated areas of Thailand.

Although there is strong evidence to suggest a relationship between urinary cadmium excretion and excretion of renal biomarkers (particularly low molecular weight proteins such as β 2-microglobulin, pHc, and retinol binding protein), there is less agreement about the significance of the early renal changes and the threshold urinary cadmium levels associated with renal damage. Several studies monitoring

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populations following a decrease in cadmium exposure have attempted to address the question of the reversibility of early renal changes. In Japan, cadmium-contaminated soil used in rice paddies was replaced resulting in decreasing urinary cadmium levels in residents consuming rice grown in these fields (Cai et al. 2001; Iwata et al. 1993; Kobayashi et al. 2008b; Sato et al. 2010). Although, cadmium exposure decreased over the same time period, the levels of renal biomarkers increased (Cai et al. 2001; Iwata et al. 1993; Kido et al. 1988; Kobayashi et al. 2008b; Sato et al. 2010) and the prevalence of abnormal values remained higher compared to the reference population (Cai et al. 2001). Although significant decreases in urinary cadmium levels were observed over time, cadmium burdens still remained high; urinary cadmium levels at the later time periods were 6.03–9.6 µg/g creatinine (Cai et al. 2001; Iwata et al. 1993; Kido et al. 1988). Kobayashi et al. (2008b) found significant correlations (after adjustment for age) between the amount of time since soil replacement and increases in urinary levels of retinol binding protein, total protein, and glucose (males only). In contrast, a follow-up study of a portion of the population examined by Buchet et al. (1990) found small, but statistically significant, decreases in urinary cadmium levels and urinary levels of β2-microglobulin, NAG, and retinol binding protein (Hotz et al. 1999). Urinary cadmium levels in this study (0.6–0.9 µg/g creatinine at baseline and 0.5–0.8 µg/g creatinine at follow up) were much lower than levels in the Japanese studies. Wu et al. (2008) examined biomarkers of renal dysfunction before (measured in 1995) and after (measured in 1998) remediation in 148 adults living in an area of China with cadmium pollution. The subjects were divided into two groups based on whether or not they had elevated β2-microglobulin levels in 1995. Among the subjects with no alteration in β2-microglobulin levels in 1995, there were no significant changes in β2-microglobulin levels in subjects with urinary cadmium levels of <10 µg/g creatinine in 1995 and significant increases in β2-microglobulin levels in the subjects with initial urinary cadmium levels of ≥10 µg/g creatinine. In the subjects with elevated β2-microglobulin levels in 1995, there were significant decreases in β2-microglobulin in subjects with urinary cadmium levels of <5 µg/g creatinine, no changes in subjects with urinary cadmium levels of 5 µg/g creatinine, and significant increases in β2-microglobulin levels in subjects with urinary cadmium levels of ≥10 µg/g creatinine. A similar pattern was found for urinary albumin levels, with significant decreases in urinary albumin levels in subjects previously diagnosed with albuminuria and urinary cadmium levels of <5 µg/g creatinine and no changes in urinary albumin levels in subjects with urinary cadmium levels of ≥5 µg/g creatinine. In subjects without albuminuria in 1995, there were increases at the higher urinary cadmium levels (5 and 20 µg/g creatinine). Although the data are inconclusive, the results of these studies provide some indication of reversibility of renal damage resulting from substantial decreases in cadmium exposure among subjects exposed to low levels of cadmium. However, renal damage may continue to progress in subjects initially exposed to higher levels of cadmium.

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A number of investigators have examined different approaches to establishing a safe cadmium body burden (as assessed by urinary cadmium levels). Several BMD analyses of data from populations living in cadmium nonpolluted areas in Sweden (Suwazono et al. 2006) or Japan (Kobayashi et al. 2006, 2008a; Suwazono et al. 2011a, 2011b, 2011c; Uno et al. 2005) or cadmium polluted areas in Japan (Shimizu et al. 2006) or China (Jin et al. 2004c) have been conducted. The analyses used urinary cadmium levels as a biomarker of cadmium exposure and the prevalence of abnormal levels of β 2-microglobulin, pHc, protein, NAG, retinol binding protein, albumin, or glomerular filtration rate as biomarkers of renal effects. Two approaches were used for BMD modeling: dichotomous variable (Jin et al. 2004c; Kobayashi et al. 2006; Shimizu et al. 2006; Uno et al. 2005) or hybrid (Kobayashi et al. 2008a; Suwazono et al. 2006, 2011a, 2011b, 2011c) approaches. In the dichotomous variable approach, urinary cadmium excretion was divided into categories and the distribution of abnormal values (exceeding the cut-off value) was fit to dichotomous BMD models. As noted by Suwazono et al. (2010), one limitation of this approach is that it does not allow for adjustment for potential covariates, particularly age; additionally, the results may fluctuate depending on the categorization of exposure, number of categories, or dose intervals. The hybrid approach eliminates the categorization of subjects by exposure (e.g., urinary cadmium levels) and is based on a continuous measure of outcome and allows for the adjustment of potential covariates such as age and BMI. As summarized in [Table 3-8](#), the BMDs for urinary cadmium levels vary widely between the studies depending on the renal biomarker and the cut-off level used. For example, when NAG is used as the effect biomarker, the BMD_{0.05} (dose associated with a 5% extra risk) values of 0.64, 12.0–10.8, and 6.36–7.74 μ g/g creatinine were calculated by Suwazono et al. (2006), Kobayashi et al. (2006), and Jin et al. (2004c) when the 95% upper limit cut-off value of 3.6, 16.0–16.6, and 15.0 U/g creatinine, respectively, was used. The results of the two BMD approaches were similar when similar cut-off levels were used. The BMDL (95% confidence bound of the BMD) is typically considered a no adverse effect level; the results of these BMD analyses suggest that chronic exposure to cadmium resulting in urinary cadmium levels of 0.3–11.31 or 0.6–11.4 μ g/g creatinine would be associated with a 5 or 10% additional risk of renal dysfunction.

Ikeda and associates used regression analysis to predict a threshold urinary cadmium level. Plotting urinary cadmium levels against β 2-microglobulin levels taken from published data from populations living in cadmium polluted and non polluted areas of Japan resulted in a distribution shaped like the letter “J”. The threshold level was defined as the point of flexion in the “J” shaped curve. In the first investigation (Ikeda et al. 2003b), the point of flexion was estimated as the point of intersection between two regression lines: one with no elevation in β 2-microglobulin from non-exposed populations and the

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Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels (µg/g Creatinine)

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Sweden) 790 females; 53–64 years old	NAG	3.6 U/g creat. (95% cut-off) ^a	Profile likelihood method	0.64	0.50	1.08	0.83	Suwazono et al. 2006
	pHC	6.8 mg/g creat. (95% cut-off) ^a		0.63	0.49	1.05	0.81	
	Estimated GFR	78.5 mL/minute (95% cut-off) ^a		1.08	0.70	1.80	1.18	
Residents in cadmium-polluted (1,397 males, 1,706 females) and cadmium nonpolluted areas (Japan) (130 males, 159 females); ≥50 years old	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off) ^b	Quantal linear model	1.5 (M) 1.4 (F)	1.2 (M) 1.1 (F)	3.1 (M) 2.9 (F)	2.5 (M) 2.3 (F)	Shimizu et al. 2006
		507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off) ^b	Log-logistic model	3.7 (M) 2.6 (F)	2.9 (M) 1.5 (F)	5.1 (M) 6.3 (F)	4.2 (M) 2.7 (F)	
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off) ^c	Quantal linear model	2.3 (M) 1.7 (F)	1.8 (M) 1.4 (F)	4.7 (M) 3.5 (F)	3.7 (M) 2.9 (F)	
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off) ^c	Log-logistic model	4.8 (M) 4.4 (F)	3.9 (M) 3.2 (F)	6.3 (M) 6.4 (F)	5.5 (M) 5.1 (F)	
Residents in cadmium-polluted (1,397 males, 1,706 females) ^d and cadmium nonpolluted areas (Japan) (520 males, 700 females); ≥50 years old	β2M	915.5 µg/g creat. (M) 897.1 µg/g creat. (F) (95% cut-off) ^e	Profile likelihood method	4.0 (M) 4.0 (F)	3.5 (M) (3.7)F)			Suwazono et al. 2011b

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Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels (µg/g Creatinine)

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Japan) 1,114 males, 1,664 females	Protein	157 mg/g creat. (M)	Log-logistic model	3.6 (M)	3.1 (M)	5.6 (M)	4.9 (M)	Kobayashi et al. 2006
		159 mg/g creat. (F)		4.8 (F)	4.2 (F)	7.5 (F)	6.6 (F)	
		(84% cut-off) ^f						
		309 mg/g creat. (M)		10.6 (M)	6.8 (M)	15.3 (M)	9.6 (M)	
	β2M	311 mg/g creat. (F)		8.7 (F)	7.3 (F)	12.0 (F)	9.9 (F)	
		(95% cut-off) ^g						
		507 µg/g creat. (M)		2.9 (M)	2.4 (M)	5.0 (M)	4.0 (M)	
		400 µg/g creat. (F)		3.8 (F)	3.3 (F)	6.6 (F)	5.5 (F)	
	NAG	(84% cut-off) ^f						
		994 µg/g creat. (M)		6.4 (M)	4.5 (M)	10.2 (M)	7.1 (M)	
		784 µg/g creat. (F)		8.7 (F)	7.3 (F)	12.0 (F)	9.9 (F)	
		(95% cut-off) ^g						
		8.2 U/g creat. (M)		4.8 (M)	3.3 (M)	8.3 (M)	5.7 (M)	
		8.5 U/g creat. (F)		4.7 (F)	3.7 (F)	8.3 (F)	6.4 (F)	
	β2M	(84% cut-off) ^f						
		16.0 U/g creat. (M)		12.0 (M)	7.7 (M)	16.4 (M)	10.3 (M)	
		16.6 U/g creat. (F)		10.8 (F)	8.5 (F)	14.8 (F)	11.4 (F)	
		(95% cut-off) ^g						
General population (Japan) 1,181 males, 1,748 females	β2M	492 µg/g creat. (M)	Multiple logistic model	3.0 (M)	2.7 (M)	5.0 (M)	4.6 (M)	Kobayashi et al. 2008a
		407 µg/g creat. (F)		3.4 (F)	3.2 (F)	5.7 (F)	5.4 (F)	
		(84% cut-off) ^h						
		965 µg/g creat. (M)		4.9 (M)	4.5 (M)	7.4 (M)	6.8 (M)	
		798 µg/g creat. (F)		5.9 (F)	5.6 (F)	8.6 (F)	8.1 (F)	
		(97.5% cut-off) ⁱ						
	β2M	1,000 µg/g creat.		5.0 (M)	4.6 (M)	7.5 (M)	6.9 (M)	
				6.7 (F)	6.3 (F)	9.4 (F)	8.9 (F)	

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Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels (µg/g Creatinine)

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Japan) 547 males, 723 females; aged ≥50 years	Protein	159 mg/g creat. (M) 93 mg/g creat. (F) (95% cut-off) ^a	Profile likelihood method	2.6 (M) 1.7 (F)	2.1 (M) 1.5 (M)			Suwazono et al. 2011c
	β2M	708 µg/g creat. (M) 415 µg/g creat. (F) (95% cut-off) ^e		3.4 (M) 1.7 (F)	2.6 (M) 1.4 (F)			
	NAG	10.7 IU/g creat. (M) 11.1 IU/g creat. (F) (95% cut-off) ^j		6.3 (M) 4.3 (F)	4.1 (M) 3.1 (F)			
	Protein	70 mg/g creat. (M) 70 mg/g creat. (F) (84% cut-off) ^k	Quantal linear model	0.9 (M) 3.2 (F)	0.6 (M) 1.8 (F)	1.9 (M) 6.6 (F)	1.2 (M) 3.6 (F)	Uno et al. 2005
	β2M	233 µg/g creat. (M) 274 µg/g creat. (F) (84% cut-off) ^k		0.5 (M) 0.9 (F)	0.4 (M) 0.8 (F)	1.0 (M) 1.8 (F)	0.7 (M) 1.3 (F)	
	NAG	2.4 U/g creat. (M) 2.5 U/g creat. (F) (84% cut-off) ^k		0.3 (M) 0.8 (F)	0.3 (M) 0.6 (F)	0.7 (M) 1.6 (F)	0.6 (M) 1.2 (F)	
General population (Japan) ^l 209 males, 215 females; 40–49 years old	Protein	67.7 mg/g creat. (M) 94.6 mg/g creat. (F) (95% cut-off) ^a	Profile likelihood method	1.3 (M) 3.2 (F)	0.9 (M) 1.9 (F)			Suwazono et al. 2011a
	β2M	224.5 µg/g creat. (M) 298.9 µg/g creat. (F) (95% cut-off) ^a		0.9 (M) 2.2 (F)	0.7 (M) 1.5 (F)			
	NAG	2.2 IU/g creat. (M) 2.1 IU/g creat. (F) (95% cut-off) ^a		0.7 (M) 1.3 (F)	0.6 (M) 0.6 (F)			

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Table 3-8. Benchmark Dose Estimations of Urinary Cadmium Levels ($\mu\text{g/g}$ Creatinine)

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Japan) ^j 201 males, 203 females; 50–59 years	Protein	94.5 mg/g creat. (M)	Profile likelihood method	1.6 (M)	1.1 (M)			Suwazono et al. 2011a
		92.7 mg/g creat. (F) (95% cut-off) ^a		5.7 (F)	3.4 (F)			
	β 2M	322.1 $\mu\text{g/g}$ creat. (M)		1.8 (M)	1.2 (M)			
		296.7 $\mu\text{g/g}$ creat. (F) (95% cut-off) ^a		2.4 (F)	1.8 (F)			
	NAG	2.5 IU/g creat. (M)		1.0 (M)	0.8 (M)			
		3.3 IU/g creat. (F) (95% cut-off) ^a		3.2 (F)	2.3 (F)			
Residents in cadmium highly polluted area (China) 123 males, 171 females Residents in cadmium moderately polluted area (China) 81 males, 162 females	NAG	15.0 U/g creat. (95% cut-off) ^m	Quantal linear logistic regression model	6.36 (M)	5.83 (M)			Jin et al. 2004c
	NAG-B	4.0 U/g creat. (95% cut-off) ^k		7.74 (F)	5.46 (F)			
				4.88 (M)	3.98 (M)			
	β 2M	800 $\mu\text{g/g}$ creat. (95% cut-off) ^m		4.24 (F)	3.70 (F)			
				5.86 (M)	4.74 (M)			
	RBP	0.300 mg/g creat. (95% cut-off) ^m		9.98 (F)	8.47 (F)			
	Albumin	0.300 mg/g creat. (95% cut-off) ^m		5.99 (M)	4.87 (M)			
				9.03 (F)	7.63 (F)			
		25.0 mg/g creat. (95% cut-off) ^m		16.72 (M)	11.18 (M)			
				14.42 (F)	11.31 (F)			

^a95th percentile of effect biomarkers on the “hypothetical” control distribution at a urinary cadmium level of zero.

^b84% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.

^c95% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.

^dSame population of residents living in polluted area as Shimizu et al. (2006).

^e95th percentile calculated by benchmark model at no cadmium exposure (urinary cadmium equal to zero), adjusted to mean age.

^f84% upper limit value of the target population of people who have not smoked.

^g95% upper limit value of the target population of people who have not smoked.

^h84th percentile level in subjects from nonpolluted areas.

ⁱ97.5th percentile level in subjects from nonpolluted areas.

^j95th percentile calculated by benchmark model at no cadmium exposure (urinary cadmium equal to zero), adjusted to mean age in females only.

^k84% upper limit value of the target population.

^lSame population as Uno et al. (2005), divided into two age groups.

^m95% upper limit value from a control group 98 males and 155 females living in a cadmium nonpolluted area.

BMD = benchmark dose; BMDL = lower 95% confidence limit on the benchmark dose; BMR = benchmark response; β 2M = β 2-microglobulin; creat. = creatinine; F = female; M = male; NAG = *N*-acetyl- β -D-glucosaminidase; NAG-B = *N*-acetyl- β -D-glucosaminidase's isoform B; RBP = retinol binding protein

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other when β 2-microglobulin was >400 or $>1,000$ $\mu\text{g/g}$ creatinine using data from exposed populations. Although no specific data were given for the two populations, the investigators noted that the highest urinary cadmium levels in the non-exposed populations were 5.6 and 3.6 $\mu\text{g/g}$ creatinine in females and males, respectively. The points of intersection of the regression lines were 11.0 and 11.7 $\mu\text{g/g}$ creatinine in females using the >400 and 1,000 $\mu\text{g/g}$ creatinine criteria, respectively, and 10.0 and 11.0 $\mu\text{g/g}$ creatinine in males. The second investigation also used published data on Japanese populations living in polluted and nonpolluted areas (Ikeda et al. 2005b). The urinary cadmium levels ranged from 0.2 to 7.8 $\mu\text{g/g}$ creatinine and from 0.8 to 31.6 $\mu\text{g/g}$ creatinine in the nonpolluted and polluted areas, respectively, and the data for the two populations were combined. Plotting urinary cadmium levels against β 2-microglobulin levels showed that there was a marked increase in β 2-microglobulin levels (levels exceeded 1,000 $\mu\text{g/g}$ creatinine) when urinary cadmium levels exceeded 4 $\mu\text{g/g}$ creatinine. The urinary cadmium levels at the point of intersection of the regression line for urinary cadmium levels of ≤ 2 or ≤ 5 $\mu\text{g/g}$ creatinine was 6.7 and 6.7 $\mu\text{g/g}$ creatinine using ordinary scales and 3.7 and 3.7 $\mu\text{g/g}$ creatinine using double logarithmic scales. These urinary cadmium levels corresponded to β 2-microglobulin levels of 139 and 267 $\mu\text{g/g}$ creatinine with the ordinary scales and 118 and 118 $\mu\text{g/g}$ creatinine using the double logarithmic scales. Using these regression equations and a critical β 2-microglobulin level of 1,000 $\mu\text{g/g}$ creatinine resulted in urinary cadmium levels of 7.6 (ordinary scales) or 8.1 (double logarithmic scales) $\mu\text{g/g}$ creatinine. Based on this analysis, the investigators concluded that at urinary cadmium levels of >4 $\mu\text{g/g}$ creatinine, there is a substantial increase in β 2-microglobulin levels (Ikeda et al. 2005b). Similarly, Kobayshi et al. (2009a) estimated the threshold level for lifetime cadmium intake using BMD modeling in 2607 adults, aged ≥ 50 years, residing for at least 30 years in an area of Japan with known cadmium contamination. A lifetime cadmium intake of 1.16–2.43 g in males and 0.86–1.79 g in women would be associated with a 5% additional risk of proteinuria and/or glucosuria.

A third approach used to identify a threshold level was a meta-analysis conducted by Gamo et al. (2006) using published data on environmentally exposed populations. Urinary cadmium was used as a biomarker of exposure and the prevalence of abnormal levels of β 2-microglobulin as an indicator of renal dysfunction. The investigators estimated maximum permissible geometric mean urinary cadmium levels in age- and gender-specific populations that would not result in a significant increase in the prevalence of abnormal β 2-microglobulin levels. They concluded that the geometric mean urinary cadmium level for a population in a small geographical area should not exceed 3 $\mu\text{g/g}$ creatinine; in a nationwide population, the geometric mean should not exceed 2 $\mu\text{g/g}$ creatinine.

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Numerous studies in rats, mice, and rabbits confirm that oral exposure to cadmium causes kidney damage including proteinuria and tubular damage (Andersen et al. 1988; Bernard et al. 1980, 1988a, 1992; Bomhard et al. 1984; Borzelleca et al. 1989; Cardenas et al. 1992a, 1992b; Cha 1987; Fingerle et al. 1982; Gatta et al. 1989; Gill et al. 1989b; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Kozłowska et al. 1993; Mangler et al. 1988; Masaoka et al. 1994; Pleasants et al. 1992, 1993; Prigge 1978a; Steibert et al. 1984; Stowe et al. 1972; Wilson et al. 1941). Histopathological findings include focal necrosis of proximal tubular epithelial cells and cloudy swelling in renal tubules (Cha 1987). Some studies have also shown no effect on renal function (Basinger et al. 1988; Borzelleca et al. 1989; Boscolo and Carmignani 1986; Groten et al. 1990; Jamall et al. 1989; Loeser and Lorke 1977a, 1977b).

In acute-duration gavage studies in rats, decreased urine flow (Kotsonis and Klaassen 1977) and histopathologic evidence of kidney damage have been reported (Borzelleca et al. 1989) at the very high doses of 150 and 138 mg/kg/day, respectively. No effect on renal function was reported in rats receiving 13.9 mg/kg/day for 10 days in drinking water (Borzelleca et al. 1989). Mice treated with a single gavage dose showed tubular necrosis at 88.8 mg/kg in one study (Andersen et al. 1988), but no effects on the kidney in another study at a dose of 112 mg/kg (Basinger et al. 1988). Proteinuria is a common finding in intermediate-duration oral exposure studies in rats (Bernard et al. 1988a; Cardenas et al. 1992a, 1992b; Kotsonis and Klaassen 1978; Prigge 1978a), as are histopathologic changes in the kidney (Gatta et al. 1989; Itokawa et al. 1974; Kotsonis and Klaassen 1978; Wilson et al. 1941). Renal clearance was decreased in one study (Kawamura et al. 1978). Both increases (Pleasants et al. 1992, 1993) and decreases (Kozłowska et al. 1993) in relative kidney weight have been reported. These effects occurred in rats at doses ranging from 2 to 30 mg/kg/day. No renal effects were seen in dogs receiving 0.75 mg/kg/day cadmium for 3 months (Loeser and Lorke 1977b), but interstitial renal fibrosis was observed in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972). Renal dysfunction has been reported in Rhesus monkeys exposed to 1.2 mg/kg/day for 9 years, but not at 0.4 mg/kg/day (Masaoka et al. 1994). Adverse renal effects are common in rats following chronic-duration oral exposure to cadmium. Proteinuria (Bernard et al. 1992; Bomhard et al. 1984) and histopathologic damage (Fingerle et al. 1982; Mangler et al. 1988) have been reported at doses ranging from 1.8 to 12.5 mg/kg/day cadmium.

The hypothesis that a critical concentration of approximately 200 µg/g in the renal cortex must be reached before proteinuria develops is generally supported by the animal data (Bhattacharyya et al. 1988c; Kotsonis and Klaassen 1978; Mangler et al. 1988; Shaikh et al. 1989; Viau et al. 1984).

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Endocrine Effects. Using data from the NHANES 1988–1994, Schwartz et al. (2003) investigated possible associations between cadmium exposure (as measured by urinary cadmium levels) and the prevalence of impaired fasting glucose and diabetes. Analysis on 8,722 participants of the survey (≥ 40 years old) showed a dose-related increase in both impaired fasting glucose and diabetes after adjusting for age, ethnicity, sex, and BMI. No other studies were located regarding endocrine effects in humans after oral exposure to cadmium.

Studies on the potential toxicity of cadmium to the endocrine system consist of studies conducting histopathologic examination of endocrine tissues and studies examining 24-hour variations in hormone release. No adverse effects were seen in parathyroid glands from female Wistar rats exposed to 8 mg Cd/kg/day via drinking water for 90 days (Kawamura et al. 1978) or in adrenal gland from male Sprague-Dawley rats exposed to 8 mg/kg/day via drinking water for 24 weeks (Kotsonis and Klaassen 1978). Pituitary, adrenals, thyroid, and thymus were unaffected in Wistar rats exposed to 3 mg/kg/day cadmium via feed for 3 months (Loeser and Lorke 1977a). Wilson et al. (1941) reported pancreatic atrophy and pancreatitis in rats from cadmium at 2.79 mg/kg/day via feed for 100 days. In rabbits exposed to 14.9 mg Cd/kg body weight/day via drinking water for 200 days, the pancreas had moderate concentrations of cadmium, but no interstitial fibrosis or other pathologic alterations (Stowe et al. 1972). Alterations in the 24-hour pattern of plasma adrenocorticotropin hormone and growth hormone levels were observed in rats exposed to 0.92 or 1.8 mg Cd/kg/day as cadmium chloride in drinking water for 30 days (Caride et al. 2010b); significant increases in adrenocorticotropin hormone and thyroid stimulating hormone levels were also observed. Cadmium also disrupted the daily pattern of aspartate, glutamate, and glutamine content in the anterior and posterior pituitary gland in rats exposed to 0.92 or 1.8 mg Cd/kg/day as cadmium chloride in drinking water for 30 days (Caride et al. 2010a).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to cadmium.

Coarse fur was reported in Long-Evans rats receiving 6.13 mg/kg/day cadmium during Gd 6–15 (Machemer and Lorke 1981). A ruffled hair coat was reported in Wistar rats receiving 40 mg/kg/day cadmium by gavage 5 days/week for 14 weeks (Baranski and Sitarek 1987). No other reports of dermal effects after oral exposure to cadmium were located.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to cadmium.

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Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cadmium.

Decreased body weight and decreased rates of growth are common findings in studies where experimental animals are orally exposed to cadmium. Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium exhibited a 12% decrease in body weight, but 100 mg/kg had no effect (Kotsonis and Klaassen 1977). Daily gavage doses of 15.3 mg/kg over a 10-day period caused a 79% decrease in body weight gain in male Sprague-Dawley rats (Borzelleca et al. 1989). Significant reductions in maternal weight gain have also been reported (Baranski 1985; Machemer and Lorke 1981).

Body weight reductions are also seen in intermediate-duration studies. For example, in a 14-week exposure via drinking water in male Long-Evans rats, 2.9 mg/kg/day had no effect on body weight gain; however, 5.8 mg/kg/day caused a 6–23% decrease and 11.6 mg/kg/day caused a 47–58% decrease (Pleasant et al. 1992, 1993). In general, intermediate-duration doses in feed or drinking water of ≤ 3 mg/kg/day have either no effect or only a small effect (10–20% decrease) on body weight in rats (Carmignani and Boscolo 1984; Jamall et al. 1989; Loeser and Lorke 1977a; Muller et al. 1988; Ogoshi et al. 1989; Perry et al. 1989; Wilson et al. 1941). Higher doses (4–14 mg/kg/day) had no effect in some studies (Kostial et al. 1993; Kotsonis and Klaassen 1978; Prigge 1978a; Viau et al. 1984) and small effects in others (Cha 1987; Kawamura et al. 1978; Kozłowska et al. 1993). A 29% decrease in maternal weight gain was observed in rats exposed to a high dose of 40 mg/kg/day (Baranski and Sitarek 1987). In mice, a dose of 4.8 mg/kg/day had no effect on maternal weight gain, but a dose of 9.6 mg/kg/day caused a 14% decrease (Webster 1978). A high dose of 232 mg/kg/day in mice caused a 29% decrease in body weight (Waalkes et al. 1993). Beagle dogs were unaffected at 0.75 mg/kg/day (Loeser and Lorke 1977b), as were rabbits at up to 2.2 mg/kg/day (Boscolo and Carmignani 1986; Tomera and Harakal 1988). A small decrease (11%) was seen in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972).

A chronic-duration study in Rhesus monkeys reported decreased growth rates at 0.4 mg/kg/day, but no effect at 0.12 mg/kg/day (Masaoka et al. 1994). No effect on body weight was seen in rats at up to 4.4 mg/kg/day (Decker et al. 1958; Fingerle et al. 1982; Mangler et al. 1988), but a small effect was seen at 7 mg/kg/day (Waalkes and Rehm 1992). Decreased terminal body weight was observed in mice after 12 months of drinking-water exposure to a high dose of 57 mg/kg/day (Hays and Margaretten 1985).

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Metabolic Effects. Hyperthermia and metabolic acidosis were reported in a human male who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

No studies were located regarding metabolic effects in animals after oral exposure to cadmium.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cadmium.

Numerous studies in rats, mice, and monkeys have established the capability of cadmium to affect the immune system, but the clinical significance of the effects is not clear. In mice, intermediate-duration oral exposure to cadmium has been shown to increase resistance to viral infection (Exon et al. 1986), to be without effect on natural or acquired resistance to infection (Bouley et al. 1984), and to increase mortality from virally-induced leukemia (Blakley 1986; Malave and de Ruffino 1984). Oral cadmium exposure has also been found to suppress the humoral immune response of mouse splenic cells to sheep red blood cell antigen in 6-week-old mice (Blakley 1985), but not in 12-month-old mice (Blakley 1988). The author suggests that “natural” age-related immune system dysfunction masked any cadmium suppressive effect in the 12-month-old mice, and that immunotoxicological investigations in aged models appear to be a poor indicator of immune response in the general population. Oral cadmium exposure has also been found to increase the cell-mediated immune response of monkeys (Chopra et al. 1984), to induce anti-nuclear antibodies in mice (Ohsawa et al. 1988), to increase circulating leukocytes in female rats (Borzelleca et al. 1989), and to exhibit time-dependent inhibitory and stimulative effects (Cifone et al. 1989b) or no effect (Stacey et al. 1988a) on natural killer cell activity in rats. The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in [Table 3-6](#) and plotted in [Figure 3-2](#).

3.2.2.4 Neurological Effects

A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure (see Section 3.8.1 for a discussion of the limitations of using hair as an indicator of exposure). End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempfer et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding

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effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate quantification of cadmium exposure.

Although cadmium-induced neurotoxicity has not been clearly demonstrated in human studies, it has been observed in animal studies. Both a single oral exposure (Kotsonis and Klaassen 1977) and intermediate-duration exposure of adult rats to cadmium resulted in significantly decreased motor activity (Kotsonis and Klaassen 1978; Nation et al. 1990). Intermediate-duration oral exposure to cadmium has also been reported to cause weakness and muscle atrophy (Sato et al. 1978), induce aggressive behavior (Baranski and Sitarek 1987), induce anxiety as manifested by increased passive avoidance behavior (Nation et al. 1984) and by increased ethanol consumption (Nation et al. 1989), and alter brain biogenic amine content and enzyme activities (Murthy et al. 1989). Doses associated with these effects range from 5 to 40 mg/kg/day cadmium. Degenerative changes in the choroid plexus have been reported in mice exposed to 1.4 mg/kg/day cadmium in drinking water for 22 weeks (Valois and Webster 1989). Peripheral neuropathy has been reported in rats after a 31-month exposure to cadmium in drinking water (Sato et al. 1978). Neurological effects in offspring of animals orally exposed to cadmium during gestation are discussed in Section 3.2.2.5. The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in [Table 3-6](#) and plotted in [Figure 3-2](#).

3.2.2.5 Reproductive Effects

Several studies have examined the possible association between increased cadmium exposure and male reproductive toxicity; however, most studies focused on sex steroid hormone levels and the results appear to be inconsistent. Akinloye et al. (2006) found significant associations between increasing blood cadmium levels and increasing levels of serum luteinizing hormone, follicle stimulating hormone, prolactin, and testosterone among infertile men (sperm counts <20 million/cm³ or no spermatozoa in semen). A significant association between increased blood cadmium levels and increased serum testosterone was also found in a group of workers with slight to moderate lead exposure (Telišman et al. 2000); however, neither study controlled for smoking. A study by Jurasović et al. (2004) found significant associations between blood cadmium levels and increased serum estradiol, follicle stimulating hormone, and testosterone levels in infertile men after adjusting for age, smoking, alcohol consumption, and biomarkers of lead, copper, zinc, and selenium. In contrast, a study of Chinese men living in areas with high levels of cadmium in rice did not find significant correlations between urinary or blood cadmium levels and serum testosterone, follicle stimulating hormone, or luteinizing hormone levels after

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adjusting for BMI, age, smoking, and alcohol consumption (Zeng et al. 2004a). However, they did find that the prevalence of abnormally elevated serum testosterone levels ($>95^{\text{th}}$ percentile for controls) increased with exposure to cadmium. Using NHANES III data, Menke et al. (2008) found significant associations between urinary cadmium levels and serum testosterone and estradiol levels, but the associations were no longer significant after adjusting from smoking status and serum cotinine levels. Differences in study populations (e.g., infertile men, background cadmium exposure, high cadmium dietary exposure) and confounding factors (e.g., smoking, lead exposure) limit the interpretation of these results.

Four studies examined the possible association between cadmium exposure and sperm quality. In infertile men, increasing serum cadmium levels were significantly associated with abnormal sperm morphology and decreased sperm counts, sperm motility, and sperm viability (Akinloye et al. 2006). Another study found significant associations between blood cadmium levels and abnormal sperm morphology and decreased sperm motility in workers with slight to moderate lead exposure (Telišman et al. 2000). As noted previously, neither study adjusted for smoking. No significant correlations between blood cadmium levels and sperm quality were observed in infertile men with or without adjustment for smoking (Jurasović et al. 2004). Similarly, no significant association between blood cadmium levels and abnormal semen parameters were observed in infertile men (Benoff et al. 2009), although seminal plasma cadmium levels were significantly negatively correlated with sperm concentration and sperm motility in whole semen. Among men exposed to high levels of environmental cadmium, blood cadmium levels were significantly higher in men with abnormal digital rectal examinations of the prostate and trend analysis showed a dose-response relationship between cadmium exposure and the prevalence of abnormal prostate specific antigen (Zeng et al. 2004b).

Data on possible reproductive toxicity of cadmium in women are limited to two studies examining the possible association between cadmium body burden and endometriosis and one study examining fecundability. Among infertile Japanese, no association between urinary cadmium levels and the risk of endometriosis was observed (Itoh et al. 2008). Jackson et al. (2008) found a significant association between blood cadmium levels and risk of endometriosis using NHANES 1999–2002 data. Blood cadmium levels were significantly higher among women with endometriosis as compared to women without endometriosis. When comparing participants with the highest tertile of blood cadmium (0.5–8.5 $\mu\text{g/L}$) with the lowest tertile (<0.3 $\mu\text{g/L}$), the multivariate (including lead and mercury blood levels, race/ethnicity, smoking status, age) adjusted odds ratio was 3.39 (95% CI of 1.37–8.40). No association between blood cadmium levels and risk of uterine myomas was found. The possible association between

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elevated cadmium body burden and time to pregnancy was examined among 400 couples participating in the Longitudinal Investigation of Fertility and the Environment (LIFE) Study (Buck Louis et al. 2012). After adjusting for several variables (age, BMI, cotinine, parity, and serum lipids), female urine cadmium levels were associated with a reduction in the fecundability odds ratio (0.78; 95% CI of 0.63–0.97) (a fecundability odds ratio of <1 denotes a longer time to pregnancy).

A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from cadmium exposure. In male rats and mice, acute oral exposure to near-lethal (60–100 mg/kg) doses can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25–50 mg/kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bomhard et al. 1987; Dixon et al. 1976).

The following intermediate-duration dosing regimens resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success: 0.25 mg Cd/kg/day via gavage for 10 weeks (Bomhard et al. 1987); 5 mg/kg/day via water for 30–90 days (Dixon et al. 1976); 2.5 mg/kg/day via food for 4 weeks (Groten et al. 1990); 8 mg/kg/day via water for 24 weeks (Kotsonis and Klaassen 1978); 3 mg/kg/day via food for 12 weeks (Loeser and Lorke 1977a, 1977b); 2.9 mg/kg/day via water for 14 weeks (Pleasant et al. 1992); and 4.64 mg/kg/day via water for 70–80 days (Zenick et al. 1982). Some dosing regimens have resulted in adverse reproductive effects. Male rats exposed to 8.58 mg Cd/kg/day in water for 10 weeks developed necrosis and atrophy of seminiferous tubule epithelium (Cha 1987). Rats exposed to 5.8 mg/kg/day via water for 14 weeks (Pleasant et al. 1992) or 11.6 mg/kg/day via water for 14 weeks (Pleasant et al. 1993) developed increased testes weight. Rats exposed to 12.9 mg/kg/day in water for 120 days developed significantly increased relative testis weight, decreased sperm count and motility, decreased seminiferous tubular diameter, and seminiferous tubular damage (pyknotic nuclei, multinucleated giant cells, interstitial edema, and dilated blood vessels) (Saxena et al. 1989). In a protocol designed to assess the effects of vitamins on cadmium toxicity, Pleasant et al. (1992, 1993) reported that vitamins A and D₃ reduced the amount of cadmium-related increase in testis weight. Bomhard et al. (1987) reported no histopathologic lesions (other than those found in control animals as part of aging) in testes of rats receiving 10 weekly doses of 5 mg Cd/kg and followed for up to 30 months.

Higher doses of cadmium were generally needed to elicit a reproductive toxic response in females compared to the males. Although a dose of 65.6 mg Cd/kg/day via gavage for 10 days was sufficient to produce testicular atrophy and loss of spermatogenic element in male rats, no effects were seen in female

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rats up to 138 mg/kg/day (Borzelleca et al. 1989). Decreased percentage of fertilized females and percentage of pregnancies were reported at 61.32 mg Cd/kg/day via gavage for 10 days during gestation (Gd 6–15) (Machemer and Lorke 1981). No effect was seen at doses up to 18.39 mg/kg/day (Machemer and Lorke 1981). Baranski (1987) also reported no treatment related effects on number or percentage of females pregnant with 28.8 mg Cd/kg/day via gavage for gestation days (Gds) 1–20. Baranski and Sitarek (1987), however, administered 40 mg/kg by gavage 5 days/week for 14 weeks to female rats and observed a significant increased duration (twice as long) of the estrus cycle starting at 7–8 weeks and persisting to 14 weeks of exposure and the termination of the experiment. This adverse effect was not seen at 4 mg/kg (Baranski et al. 1983; Baranski and Sitarek 1987).

Petering et al. (1979) exposed female rats to either 2.61 mg/kg/day via drinking water for 60 days prior to gestation or during gestation, or 5.23 mg/kg/day via drinking water for 111 days including 90 days prior gestation plus 21 days during gestation. These doses had no significant effects compared with controls for the number of pups stillborn. Pond and Walker (1975) also observed no effects in females from a cadmium exposure of 19.7 mg/kg/day via food for 21–25 days, including Gd 1 through lactation day (Ld) 1, on number of pups born. No effects from a cadmium exposure on number of pups born to females were observed for an exposure of 8.2 mg/kg/day via food for 15 days, including Gd 6–20 (Sorell and Graziano 1990).

A dose of 10 mg Cd/kg/day once a day via gavage for 9 weeks (6 weeks prior to gestation and 3 weeks of gestation) significantly decreased the number of copulating and pregnant females, and the number of implants and live fetuses (Sutou et al. 1980). No effect was seen at 1 mg/kg/day (Sutou et al. 1980).

Reproductive effects on both male and female rats orally exposed to 2.5 mg/kg/day via drinking water for 180 days may have resulted in the observed decrease in litter size and increased interval between litters. Both males and females were treated over two generations. Three of five pairs failed to breed in the second generations (Schroeder and Mitchener 1971). No histopathologic lesions were found in testes or uteri of dogs given cadmium chloride at 0.75 mg/kg/day via food for 3 months (Loeser and Lorke 1977b).

Male rats were exposed to 0–14 mg Cd/kg/day via food for 77 weeks. The incidence of prostatic hyperplasias was increased above controls (1.8%) from the 3.5 mg Cd/kg/day dose. The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic proliferative lesions. Testicular

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tumors (exclusively benign interstitial tumors) increased significantly only at the highest-dose cadmium with diets adequate in zinc. Male Wistar rats exposed to cadmium in the drinking water at 0, 25, 50, 100, or 200 ppm developed tumors of the prostate (50 ppm), testes (200 ppm), and hematopoietic system (50 ppm), while dietary zinc deficiency has complex, apparently inhibitory effects on cadmium carcinogenesis by this route (Waalkes and Rehm 1992).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in [Table 3-6](#) and plotted in [Figure 3-2](#).

3.2.2.6 Developmental Effects

There are very limited data on the developmental effects of cadmium in humans. Several studies have examined the possible relationship between maternal cadmium levels and newborn size. No significant association between maternal blood cadmium levels and newborn body weight were observed in women with mean blood cadmium levels of 0.7 µg/L (Mokhtar et al. 2002), 1.04 µg/L (Nishijo et al. 2004b), 1.4 µg/L (Galicía-García et al. 1997), or 1.72 µg/L (Zhang et al. 2004) or urinary cadmium levels of >2 nmol/mmol creatinine (Nishijo et al. 2002); the Nishijo et al. (2002, 2004b), and Zhang et al. (2004) studies used statistical adjustments for maternal age, maternal size, and/or gestation age. Two studies found an association between cord blood cadmium levels and decreasing birthweight (Galicía-García et al. 1997; Salpietro et al. 2002); however, the association was only statistically significant in the Salpietro et al. (2002) study. A significant association between newborn height and maternal blood cadmium levels was observed in women with a mean blood cadmium level of 9.29 nmol/L (Nishijo et al. 2004b); other studies have not found this association (Mokhtar et al. 2002; Nishijo et al. 2002; Zhang et al. 2004). Nishijo et al. (2002) found a significant negative correlation between maternal urinary cadmium levels and gestation length; Mokhtar et al. (2002) did not find a significant association between maternal blood cadmium levels and gestation length.

Urinary cadmium content was measured in women 3 days after giving birth and compared to smoking habits and birth weight of offspring. Among nonsmoking women, when cadmium content was expressed as µg/L, cadmium levels were higher in women with infants of below-normal birth weight. However, when cadmium content was expressed as µg/g creatinine, cadmium levels were lower in women with infants with below-normal birth weight. Cadmium levels in smoking women were lower in both µg/L and µg/g in women with infants with below-normal birth weight (Cresta et al. 1989).

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Cao et al. (2009) examined the possible association between postnatal exposure to cadmium (as measured by blood cadmium) and neurodevelopment in children participating in the Treatment of Lead-Exposed Children trial. Blood cadmium levels in the children were comparable to levels in the NHANES 2005–2006 survey, and blood lead levels were between 20 and 44 µg/dL at referral. No significant associations (after adjustment for multiple variables including parent's education, gender, and concurrent blood lead levels) between blood cadmium levels and scores on neuropsychological and behavioral tests were found in children evaluated at age 5 and 7 years or IQ evaluated at 2, 5, and 7 years of age.

A number of studies in rats and mice indicate that cadmium can be fetotoxic from oral exposures prior to and during gestation. This fetotoxicity is most often manifested as reduced fetal or pup weights (Ali et al. 1986; Baranski 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Petering et al. 1979; Pond and Walker 1975; Sorell and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988), but malformations, primarily of the skeleton, have been found in some studies (Baranski 1985; Machemer and Lorke 1981; Schroeder and Mitchener 1971). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the 1–20 mg/kg/day range.

The most sensitive indicator of developmental toxicity of cadmium in animals appears to be neuro-behavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months (Baranski et al. 1983). Pups from dams exposed to 0.7 mg/kg/day during gestation had significant delays in cliff aversion and swimming behavior. Locomotor activity was significantly increased. In post-weaning measurements, locomotor activity was significantly decreased in treated groups at 60 days of age; conditioned avoidance behavior was also significantly decreased when tested at 60 and 90 days of age (Ali et al. 1986).

Nagymajtenyi et al. (1997) also reported behavioral and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. Three consecutive generations of Wistar rats were orally treated by gavage with 3.5, 7.0, or 14.0 mg Cd/kg bw (as cadmium chloride diluted in distilled water) over the period of pregnancy, lactation, and 8 weeks after weaning. Behavioral (open field behavior) and electrophysiological (spontaneous and evoked cortical activity, etc.) parameters of male rats from each generation were investigated at the age of 12 weeks. The main behavioral outcomes were increased

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vertical exploration activity (rearing) and increased exploration of an open-field center. The spontaneous and evoked electrophysiological variables showed dose- and generation-dependent changes (increased frequencies in the electrocorticogram, lengthened latency and duration of evoked potentials, etc.) signaling a change in neural functions. The results indicate that low-level, multigeneration exposure of rats to inorganic cadmium can affect nervous system function.

Desi et al. (1998) continued the above studies to further evaluate cadmium associated changes in behavior and neurological function in rats following different dosage regimens during pregnancy. Female Wistar rats were given 3.5, 7.0, or 14.0 mg Cd/kg body weight (cadmium chloride dissolved in distilled water) in three different treatment regimes: days 5–15 of pregnancy; days 5–15 of pregnancy + 4 weeks of lactation; and days 5–15 of pregnancy + 4 weeks of lactation followed by the same oral treatment of male rats of the F₁ generation for 8 weeks. The behavioral (open-field exploration) and electrophysiological (electrocorticogram, cortical-evoked potentials, conduction velocity and refractory periods of a peripheral nerve) parameters of F₁ male rats exposed by various treatments were investigated at the age of 12 weeks. The results indicate that cadmium altered the spontaneous and evoked electrophysiological functions (e.g., increased the frequency of the electrocorticogram, lengthened the latency and duration of evoked potentials, etc.) in a dose- and duration-dependent manner. Only combining treatment during the prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical exploratory activity and a significantly lower exploration frequency of the open-field center. The results suggest that low-level pre- and postnatal inorganic cadmium exposure affects the electrophysiological and higher order functions of the nervous system.

Neurochemical alterations have also been observed in the offspring of rats administered cadmium acetate in drinking water during gestation (1.12 mg Cd/kg/day) and lactation (2.41 mg Cd/kg/day) (Antonio et al. 2010). The alterations included decreased serotonin in dorsal hippocampus and dihydroxyphenylacetic acid in brain cortex and rostral neostriatum and increased 5-hydroxyindolacetic acid in dorsal hippocampus and brain cortex and glutamate in the dorsal hippocampus.

A study by Gupta et al. (1993) examined the developmental profiles of DNA, RNA, proteins, DNA synthesis, thymidine kinase activity, and concentrations of zinc and cadmium in the brain of neonates from dams exposed to cadmium acetate at 5–6.3 mg/kg/day in drinking water during gestation, and 7–8 mg/kg/day during a 21-day lactation period. Pup brain and body weights were significantly decreased in the cadmium exposed pups on Ld 7–21. Cadmium brain accumulation was significantly increased in exposed pups on Ld 7 and remained at similar levels on Ld 14 and 21. DNA and thymidine kinase brain

levels were significantly decreased in treated pups compared with controls on Ld 7, 14, and 21. The toxicological significance of changes in DNA incorporation and thymidine kinase activity are uncertain.

Xu et al. (1993b) determined lipid peroxide (LPO) concentrations in rat pups in various organs as an index of cadmium toxicity. Male and female Wistar mice were exposed to cadmium in drinking water at 0, 5.7, or 14.25 mg/kg/day for 2 months prior to mating. The pregnant females continued to be exposed during gestation and lactation. Litter size and pup survival rates were unaffected by cadmium. Body weights were not statistically different between the exposed and control groups. In pups, brain weights (at 5.7 and 14.25 mg/kg/day) and liver, kidney, and heart weights (at 14.25 mg/kg/day) were significantly decreased. Although the relative organ weights were lower in the high-dose group, the difference from controls was not statistically significant. LPO concentrations in all organs were significantly increased in pups on Ld 7 at 14.25 mg/kg/day except in the kidney; concentrations in the liver, heart, and brain were 131.5, 156, and 237.4%, respectively, of the concentrations in controls.

In contrast to most of the study results, Saxena et al. (1986) reported no developmental effects from an exposure to 21 mg Cd/kg/day via drinking water during gestation (Gd 0–20). This study evaluated simultaneous exposure to lindane (20 mg lindane/kg via gavage on Gd 6–14) and cadmium acetate in drinking water at doses that individually did not cause maternal or developmental effects. Maternal toxicity (significantly decreased weight gain) and developmental toxicity were only observed in the cadmium plus lindane group. Fetal body weight was significantly decreased; intrauterine death and the rate of skeletal anomalies were significantly increased. Anomalies consisted of decreased ossification, wavy ribs, and scrambled sternebrae.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in [Table 3-6](#) and plotted in [Figure 3-2](#).

3.2.2.7 Cancer

Epidemiology studies have examined the possible association between exposure to elevated levels of cadmium and overall cancer rates or specific cancer rates. Older studies have examined cancer rates among residents of cadmium polluted areas but did not estimate cadmium exposure levels. No significant increase in cancer rates was found among residents of a cadmium-polluted village in England (Inskip et al. 1982) or in prostate, kidney, or urinary tract cancer among residents of a cadmium-polluted area of Belgium (Lauwerys and De Wals 1981). Another study found that the geographic distribution of elevated

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rates of prostate cancer incidence paralleled the distribution of elevated cadmium concentrations in water, soil, or grain crops in Alberta, Canada (Bako et al. 1982). In a retrospective mortality study of residents of three areas of Japan classified on the basis of rice cadmium content as highly polluted, slightly polluted, or nonpolluted, no significant differences were found in mortality from cancer of all sites including prostate cancer (Shigematsu 1984). Inhabitants of cadmium-polluted areas of Japan with elevated urinary retinol binding protein excretion had a mortality rate from malignant neoplasms no different from expected (Nakagawa et al. 1987).

Three more recent studies of populations living in cadmium-polluted areas have used blood or urine to examine dose-response relationships for carcinogenic risk. Among residents living in a cadmium-polluted area of China, significantly higher blood cadmium levels were observed in subjects with suspected prostate cancer (based on digital rectal examination) as compared to subjects with normal digital rectal examination results (Zeng et al. 2004); there were no significant differences in urinary cadmium levels. However, a significant trend was found for the number of cases with positive prostate-specific antigen levels and urinary cadmium levels. In a study of residents living in an area of Japan that previously had high levels of cadmium contamination, a significant increase in cancer mortality was observed among subjects with urinary β 2-microglobulin levels of $\geq 1,000$ $\mu\text{g/g}$ creatinine (Arisawa et al. 2001); however, no increases in cancer incidence were observed in exposed subjects or in subjects with elevated urinary β 2-microglobulin, urinary cadmium, or blood cadmium levels. In a follow-up study that extended the observation period from 15 to 23 years, no alterations in cancer mortality or cancer incidence were observed in the exposed population as compared to referent populations (Arisawa et al. 2007b). However, when the subjects were divided into two groups based on urinary β 2-microglobulin levels, the relative risk of cancer deaths in males and females with β 2-microglobulin levels of $\geq 1,000$ $\mu\text{g/g}$ creatinine was 2.58 (95% CI of 1.25–5.36) compared to residents with urinary β 2-microglobulin levels of $< 1,000$ $\mu\text{g/g}$ creatinine.

Several case-control studies have examined the possible association between cadmium body burden and increased risk of cancer among the general populations. In a study conducted in Belgium, a significant relationship between bladder cancer and blood cadmium levels was reported (Kellen et al. 2007). After adjustment for age, gender, occupational exposure to polyaromatic hydrocarbons or aromatic amines, and smoking, the odds ratio was 5.7 (95% CI of 3.3–9.9) when comparing the risk of bladder cancer for subjects in the highest blood cadmium tertile to those in the lowest tertile. Another case-control study examined the possible relationship between urinary cadmium levels and breast cancer risk in the United States (McElroy et al. 2006). The breast cancer risk (after adjustment for a number of variables including

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age, parity, family history of breast cancer and BMI) in women with urinary cadmium levels in the highest quartile was 2.29 (95% CI of 1.3–4.2) as compared to women in the lowest quartile; the investigators noted that adjusting for smoking status did not change the risk estimate. Similarly, a significant increase in the risk of breast cancer was observed among women living in Long Island, New York with urinary cadmium levels $>0.60 \mu\text{g cadmium/g creatinine}$, as compared to women with urinary cadmium levels of $<0.22 \mu\text{g cadmium/g creatinine}$ after controlling for age, menopausal status, smoking and alcohol use, and family history (Gallagher et al. 2010). Another study of residents of the East Nile Delta region in Egypt with pancreatic cancer found a significant association between pancreatic cancer risk and serum cadmium levels; the odds ratio was 1.12 (95% CI of 1.04–1.23) (Kriegel et al. 2005). The study also found a significant association between farming and risk of pancreatic cancer. The results of this study should be interpreted cautiously since the study did not adjust for smoking status or farming occupation.

In a Swedish population-based study of postmenopausal women, an increased risk of endometrial cancer was found in women with elevated cadmium intake (Åkesson et al. 2008). Among women who never smoked, did not use postmenopausal hormones, had a BMI of $<27 \text{ kg/m}^2$, and consistently had a cadmium intake above the median intake for the study, the relative risk of endometrial cancer was 2.86 (95% CI of 1.05–7.79).

One study examined cadmium, zinc, and copper in human kidney tumors and normal kidneys. Kidneys with renal cell carcinoma in cortex from 31 cases (20 men and 11 women) were compared to kidneys of patients who had died from causes other than a malignant disease from 17 controls (9 men and 8 women). No patients in this study had been occupationally exposed. Smoking habits for patients were recorded. The level of cadmium in tumor tissue did not correlate with cadmium in cortex or medulla in the same kidney. No significant difference was found between cases and controls, although smoking cases had higher levels of cadmium. It was concluded that cadmium was not a risk factor for renal cell carcinoma (Hardell et al. 1994).

In rats and mice, earlier studies on chronic oral exposure to cadmium did not report an increased overall cancer incidence or the incidence of specific tumor types (Kanisawa and Schroeder 1969; Levy and Clack 1975; Levy et al. 1975; Löser 1980; Mangler et al. 1988; Schroeder et al. 1964, 1965). However, maximum daily doses tested were only 1 mg/kg/day in mice (Schroeder et al. 1964) and 3.5 mg/kg/day in rats (Löser 1980) and, in most of these studies, histopathologic examination was limited compared to contemporary standards. Löser (1980) did perform a relatively thorough histological examination. A few

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additional animal studies of noncancer effects of chronic-duration oral cadmium exposure have indicated that no dose-related increases in tumors were found at maximum doses of 4.01 mg/kg/day in rats (Fingerle et al. 1982) or 8 mg/kg/day in mice (Watanabe et al. 1986).

Waalkes and Rehm (1992) evaluated the effects of chronic dietary zinc deficiency on oral cadmium carcinogenesis in male Wistar rats. Rats were exposed for 77 weeks to cadmium at 0, 1.75, 3.5, 7.0, or 14.0 mg cadmium/kg/day as cadmium chloride in a diet containing an adequate or a deficient amount of zinc. A significant increase in the incidence of proliferative lesions (hyperplasia and adenomas) was observed in the prostate of rats exposed to 1.75 mg cadmium/kg/day in the zinc-adequate (22.7%) or zinc-deficient (15.4%) groups, as compared to controls (1.9%). However, the incidences of prostatic lesions were not significantly increased in rats exposed to higher cadmium doses. The incidence of large granular lymphocyte leukemia was significantly increased in rats fed the zinc-adequate diet with 3.5 or 7.0 mg cadmium/kg/day, but not at 14.0 mg cadmium/kg/day; however, an increased incidence was observed at 14.0 mg cadmium/kg/day in the zinc-deficient rats. Exposure to 14.0 mg cadmium/kg/day also resulted in a significant increase in interstitial cell tumors of the testes in the group fed a zinc-adequate diet. The results of the study suggest that dietary zinc deficiency may inhibit the carcinogenic potential of cadmium, but additional research is needed.

A subsequent study by Waalkes et al. (1993) using male B6C3F1 mice evaluated the effects of cadmium exposure on tumor incidence at various times after the initiation of the carcinogenic process. The possible role of metallothionein in the susceptibility of transformed cells to cadmium cytotoxicity was also evaluated. At 5 weeks of age, mice received an intraperitoneal injection of *N*-nitrosodiethylamine (NDEA) at 90 mg/kg. At 2, 4, 8, 16, or 32 weeks post-NDEA injection, mice received water containing 1,000 ppm cadmium *ad libitum* for up to 48 weeks of post-NDEA exposure. Cadmium exposure caused a marked "reduction" in liver tumor incidence in NDEA-treated mice even when given as late as 32 weeks after the initial NDEA treatment. Cadmium alone eliminated the spontaneously occurring incidence of liver tumors (i.e., 0 of 25 compared with 5 of 25 in the controls). Liver tumors produced by NDEA were typically basophilic adenomas. Cadmium resulted in a modest reduction in lung tumor incidence, statistically significant (28% reduction) only for the 16–48-week cadmium-treated group pretreated with NDEA. Lung tumors were typically adenomas of alveolar cell origin. Cadmium alone eliminated spontaneously occurring lung tumors compared with the controls. Cadmium significantly reduced the multiplicity of tumors induced by NDEA. NDEA alone typically induced seven tumors per lung, while NDEA plus cadmium treatment reduced the number of tumors to 2.5–3.5 (data taken from a graph) with some cases showing an 80% reduction in tumor numbers. Lung tumors found in the cadmium plus

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NDEA-treatment groups were also smaller in overall size than those found in the NDEA-only treatment groups. Relatively little metallothionein was present in liver carcinomas, liver adenomas, and lung adenomas as indicated by immunohistochemistry. This finding was confirmed biochemically for the liver tumors. The authors concluded that cadmium can effectively “impair” tumor formation in the lungs and liver of male B6C3F1 mice and that cadmium appears to be able to selectively destroy existing preneoplastic and/or tumor cells (adenomas). The mechanism may involve a reduced activity and responsiveness of the metallothionein system in transformed liver cells.

A two-stage initiation/promotion experiment evaluated the promoting effects of cadmium chloride in the drinking water in rats. Cadmium exposure resulted in the following alterations in tumorigenic outcome: in the liver, hepatocellular carcinomas (initiated with diethyl nitrosamine) were decreased; in the stomach, tumors (initiated with *N*-methyl-*N'*-nitro-nitrosoguanidine plus NaCl at 10% in the diet) were not affected; in the kidney, tumors (initiated with *N*-ethyl-*N*-hydroxyethyl nitrosamine) showed increased dysplastic foci but no increase in renal cell tumors; in the pancreas, tumors (initiated with *N*-nitrosobis [2-oxopropyl] amine) had a nonsignificant increase in adenocarcinomas (female hamster study); and in the skin (initiated with 7,12-dimethyl benz(a)anthracene), there was no effect (female SENCAR mouse study) (Kurokawa et al. 1989).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to cadmium.

Some guinea pigs died 2 or 6 weeks after being exposed in a skin depot (3.1 cm²) to 2 mL of 0.239 molar aqueous of cadmium chloride (0.14 mg/kg body weight) (Wahlberg 1965). However, it is difficult to attribute these deaths to cadmium exposure, due to the low dose compared to oral LD₅₀ values and to the fact that no necropsy was done to determine whether the exposed guinea pigs might have died from pneumonia (which killed some control guinea pigs) (Wahlberg 1965).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to cadmium.

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Dermal Effects. Among eczema patients routinely patch-tested with 2% cadmium chloride, 25 out of 1,502 showed some reaction (Wahlberg 1977). Since no reaction was found at lower dilutions in reactive patients (Wahlberg 1977), the effect was likely direct irritation of the skin and is indicated as a LOAEL value in [Table 3-9](#).

No studies were located regarding dermal effects in animals after dermal exposure to cadmium.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cadmium.

Rats exposed to high concentrations of cadmium pigments or cadmium oxide in air had excessive lacrimation four hours after exposure (Rusch et al. 1986), possibly due to a direct irritation effect on the eyes.

3.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposure to cadmium does not appear to affect the immune system significantly. One report of workers with extensive exposure to cadmium dust reported an increase in complaints of eczema (Friberg 1950); however, no subsequent studies have confirmed any association. Routine patch tests among dermatitis and eczema patients using up to 2% cadmium chloride solutions have found skin irritation at 2%, but no evidence of allergic reactions at a dose of 1% among people without known prior cadmium exposure (Rudzki et al. 1988; Wahlberg 1977) or among workers occupationally exposed to cadmium (Rudzki et al. 1988). Individuals with yellow tattoos containing cadmium sulfide often experience swelling of the surrounding skin on exposure to ultra violet (UV) irradiation (Bjornberg 1963); however, this may be the result of dermal damage from the photoconductivity of cadmium sulfide rather than a direct immunological reaction.

Guinea pigs showed no contact sensitization following intradermal or topical exposure to cadmium chloride at concentrations up to 0.5% (Wahlberg and Boman 1979). The NOAEL values from each reliable study for immunological effects in each species and duration category are recorded in [Table 3-9](#).

Table 3-9 Levels of Significant Exposure to Cadmium - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
			NOAEL	Less Serious		
ACUTE EXPOSURE						
Systemic Human	once	Dermal	1	2	Wahlberg 1977 CdCl2	
			Percent (%)	Percent (%)		
Rat (Sprague- Dawley)	2 hr	Ocular	99	(excessive lacrimation)	Rusch et al. 1986 CdSeS	(eyes closed from exposure)
			mg/m³	mg/m³		
Immuno/ Lymphoret Human	once		97	(excessive lacrimation)	Rudzki et al. 1988 CdCl2	
			Percent (%)	Percent (%)		

 hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

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No studies were located regarding the following health effects in humans or animals after dermal exposure to cadmium:

3.2.3.4 Neurological Effects**3.2.3.5 Reproductive Effects****3.2.3.6 Developmental Effects****3.2.3.7 Cancer****3.3 GENOTOXICITY**

The genotoxic potential of cadmium has been studied in *in vivo* studies of cadmium workers, members of the general population, and rodents as summarized in [Table 3-10](#). Although not always consistent, these results suggest that cadmium is a clastogenic agent, as judged by the induction of DNA damage, micronuclei, sister chromatid exchange (SCE), and chromosomal aberrations.

Palus et al. (2003) examined peripheral lymphocytes from workers occupationally exposed to cadmium and found statistically significant increases compared to the control population in micronuclei rates and sister chromatid exchanges as well as evidence of an increased incidence of leukocytes with DNA fragmentation. Examination of lymphocytes and leukocytes from workers occupationally exposed to cadmium and lead or to cadmium, lead, and zinc showed increased frequency of chromosomal aberrations compared to control groups (Abraham et al. 2011; Bauchinger et al. 1976; Deknudt and Leonard 1975; Deknudt et al. 1973), but this effect was not observed in men exposed primarily to cadmium (Bui et al. 1975; O'Riordan et al. 1978). Human lymphocytes from individuals inhabiting cadmium-polluted areas of China have been found to have increased micronuclei rates and a higher frequency of chromosomal aberrations and severe aberration types, in comparison to control populations with either no known exposure to cadmium or low-level exposure (Fu et al. 1999; Tang et al. 1990). Bui et al. (1975) examined blood samples from four female Japanese patients with Itai-Itai disease and found no evidence to indicate that cadmium is capable of inducing chromosomal damage.

For the most part, cadmium exposure via inhalation (Valverde et al. 2000), oral (Devi et al. 2001; Kasuba et al. 2002), and parenteral (Fahmy and Aly 2000; Kasuba et al. 2002; Mukherjee et al. 1988a; Saplakoglu et al. 1997; Wronska-Nofer et al. 1999; Zhou et al. 2004b) routes has been shown to be associated with DNA damage and induction of micronuclei in rodent cells.

Table 3-10. Genotoxicity of Cadmium *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberrations	+	Deknuds et al. 1973
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Deknuds and Leonard 1975
Human lymphocytes	Chromosomal aberrations	+	Bauchinger et al. 1976
Human lymphocytes	Chromosomal aberrations	–	O’Riordan et al. 1978
Human lymphocytes	Chromosomal aberrations	+	Alessio et al. 1993
Human lymphocytes	Chromosomal aberrations	+	Abraham et al. 2011
Human lymphocytes	Sister chromatid exchanges	+	Abraham et al. 2011
Human lymphocytes	Sister chromatid exchanges	+	Palus et al. 2003
Human lymphocytes	Micronuclei	+	Palus et al. 2003
Human lymphocytes	DNA damage	+	Palus et al. 2003
Mouse bone marrow	DNA damage	+	Valverde et al. 2000
Mouse brain cells	DNA damage	+	Valverde et al. 2000
Mouse testicular cells	DNA damage	+	Valverde et al. 2000
Mouse liver cells	DNA damage	+	Valverde et al. 2000
Mouse kidney cells	DNA damage	+	Valverde et al. 2000
Mouse lung cells	DNA damage	+	Valverde et al. 2000
Mouse nasal epithelial cells	DNA damage	+	Valverde et al. 2000
Oral exposure:			
Rat bone cells	Altered gene expression	+	Ohba et al. 2007
Mouse bone marrow	Chromosomal aberrations	–	Deknuds and Gerber 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988b
Rat bone marrow	Chromosomal aberrations	–	Desi et al. 2000
Human leukocytes	Chromosomal aberrations	+	Shiraishi and Yoshida 1972
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Tang et al. 1990
Human lymphocytes	Chromosomal aberrations	+	Fu et al. 1999
Mouse leukocytes	DNA damage	+	Devi et al. 2001
Rat lymphocytes	DNA damage	+	Kasuba et al. 2002
Rat spermatogenesis	Dominant lethal mutations	–	Sutou et al. 1980
Rat spermatogenesis	Dominant lethal mutations	–	Zenick et al. 1982
Rat lymphocytes	Micronuclei	+	Kasuba et al. 2002
Human lymphocytes	Micronuclei	+	Fu et al. 1999
Intraperitoneal exposure:			
Mouse oocytes	Aneuploidy	–	Mailhes et al. 1988
Mouse spermatocytes	Chromosomal aberrations	+	Selypes et al. 1992

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Table 3-10. Genotoxicity of Cadmium *In Vivo*

Species (test system)	End point	Results	Reference
Mouse bone marrow	Chromosomal aberrations	+	Fahmy and Aly 2000
Mouse spermatocytes	Chromosomal aberrations	+	Fahmy and Aly 2000
Mouse bone marrow	Chromosomal aberrations	–	Bruce and Heddle 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988a
Mouse spermatocytes	Chromosomal translocations	–	Gillivod and Leonard 1975
Rat lung cells	DNA strand breaks	+	Saplakoglu et al. 1997
Rat kidney cells	DNA strand breaks	+	Saplakoglu et al. 1997
Rat liver cells	DNA strand breaks	–	Saplakoglu et al. 1997
Mouse spermatogenesis	Dominant lethal mutations	–	Epstein et al. 1972
Mouse spermatogenesis	Dominant lethal mutations	–	Gillivod and Leonard 1975
Mouse oocytes	Dominant lethal mutations	–	Suter 1975
Rat lymphocytes hprt locus	Gene mutation	±	Jianhua et al. 2006
Mouse bone marrow	Micronuclei	±	Mukherjee et al. 1988a
Mouse bone marrow	Micronuclei	+	Wronska-Nofer et al. 1999
Mouse bone marrow	Micronuclei	+	Fahmy and Aly 2000
Mouse bone marrow	Sister chromatid exchanges	+	Mukherjee et al. 1988a
Mouse bone marrow	Sister chromatid exchanges	+	Fahmy and Aly 2000
Mouse spermatozoa	Sperm morphology	–	Bruce and Heddle 1979
Mouse spermatozoa	Sperm morphology	+	Mukherjee et al. 1988a
Syrian hamster embryo cells	Transformation	+	DiPaulo and Castro 1979
Subcutaneous exposure:			
Mouse testicular cells	Altered gene expression	+	Zhou et al. 2004b
Mouse blastocysts	Aneuploidy	+	Watanabe and Endo 1982
Syrian hamster oocytes	Aneuploidy	+	Watanabe et al. 1979
Mouse bone marrow	Chromosomal aberrations	+	Karmakar et al. 1998
Mouse testicular cells	DNA damage	–	Zhou et al. 2004b
Rat lymphocytes	DNA damage	+	Kasuba et al. 2002
Rat lymphocytes	Micronuclei	+	Kasuba et al. 2002
Mouse bone marrow	Sister chromatid exchanges	–	Nayak et al. 1989
Mouse fetal liver and lung cells	Sister chromatid exchanges	–	Nayak et al. 1989

– = negative result; + = positive result; ± = weakly positive result; DNA = deoxyribonucleic acid

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Evidence of the potential for cadmium to induce SCE (Fahmy and Aly 2000; Mukherjee et al. 1988a; Nayak et al. 1989) and chromosomal aberrations (Bruce and Heddle 1979; Desi et al. 2000; DiPaulo and Castro 1979; Fahmy and Aly 2000; Karmakar et al. 1998; Mukherjee et al. 1988a; Tang et al. 1990; Watanabe et al. 1979) is mixed. Data regarding the aneugenic potential of cadmium are limited and also conflicting. Watanabe and Endo (1982) observed an increased incidence of mouse blastocysts with trisomies and triploidies from female mice treated subcutaneously with cadmium compared to control mice. Watanabe et al. (1979) reported that subcutaneous exposure to cadmium induced mutagenicity in hamster oocytes, and in particular, induced the production of diploid oocytes. However, Mailhes et al. (1988) did not observe an increased incidence of hyperploid oocytes in female mice treated with cadmium via intraperitoneal injection.

No evidence for germ cell mutations (the dominant lethal test) has been observed in male rats orally exposed to cadmium (Sutou et al. 1980; Zenick et al. 1982) or in mice exposed to cadmium via inhalation (Gilliavod and Leonard 1975; Suter 1975) or intraperitoneal exposure (Epstein et al. 1972). However, chromosomal aberrations in mouse spermatocytes and Syrian hamster oocytes (Fahmy and Aly 2000; Selypes et al. 1992; Watanabe et al. 1979) and altered gene expression in mouse testicular cells (Zhou et al. 2004b) have been observed following cadmium exposure.

Data based on *in vitro* examination of the genotoxic effects of cadmium in microorganisms, yeast, insects, and mammalian cells are summarized in [Table 3-11](#). For the most part, *in vitro* data support the *in vivo* data suggesting that cadmium has the potential to induce DNA damage, micronuclei, chromosomal aberrations, and genetic mutations.

In vitro studies have shown that cadmium induces genetic mutations in hamster and mouse cells (Amacher and Paillet 1980; Filipic and Hei 2004; Honma et al. 1999; Jianhua et al. 2006; Oberly et al. 1982), transformation in rodent cells (Casto et al. 1979; Terracio and Nachtigal 1988), unscheduled DNA synthesis in rat cells (Denizeau and Marion 1989), DNA breaks in human cells (Depault et al. 2006; Lopez-Ortal et al. 1999; Mikhailova et al. 1997), DNA lesions in hamster cells (Jianhua et al. 2006), and inhibits DNA repair in human and hamster cells (Lutzen et al. 2004; Lynn et al. 1997). Misra et al. (1998) did not observe DNA damage in rat cells following treatment with cadmium, but DNA damage has been noted in human cells (Fatur et al. 2002; Rozgaj et al. 2002).

Chromosomal aberrations following cadmium exposure have been observed in Chinese hamster ovary cells (Cai and Arenaz 1998; Deaven and Campbell 1980; Rohr and Bauchinger 1976), but studies on

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Table 3-11. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Bacillus subtilis</i>	DNA repair	No data	±	Nishioka 1975
<i>B. subtilis</i>	DNA repair	No data	±	Kanematsu et al. 1980
<i>Salmonella typhimurium</i> (plate incorporation)	Gene mutation	–	–	Bruce and Heddle 1979
<i>S. typhimurium</i> (liquid suspension)	Gene mutation	–	–	Milvy and Kay 1978
<i>S. typhimurium</i> (liquid suspension)	Gene mutation	No data	±	Mandel and Ryser 1984
<i>S. typhimurium</i> (plate incorporation)	Gene mutation	–	+	Wong 1988
Eukaryotic organisms:				
Yeast:				
<i>Saccharomyces cerevisiae</i>	Gene mutation	No data	+	Putrament et al. 1977
<i>S. cerevisiae</i>	Intrachromosomal recombination	No data	+	Schiestl et al. 1989
Insects:				
<i>Drosophila melanogaster</i>	Dominant lethal mutations	No data	+	Vasudev and Krishnamurthy 1979
<i>D. melanogaster</i>	Nondisjunction	No data	–	Ramel and Magnusson 1979
<i>D. melanogaster</i>	Sex-linked recessive lethal mutations	No data	–	Inoue and Watanabe 1978
Mammalian cells:				
Mouse spleen cells	Chromosomal aberration	No data	+	Fahmy and Aly 2000
Chinese hamster ovary Hy cells	Chromosomal aberration	No data	+	Rohr and Bauchinger 1976
Chinese hamster ovary CHO cells	Chromosomal aberration	No data	+	Deaven and Campbell 1980
Chinese hamster ovary CHO cells	Chromosomal aberration	No data	+	Cai and Arenaz 1998
Human leukocytes	Chromosomal aberrations	No data	+	Shiraishi et al. 1972
Human blood lymphocytes	Chromosomal aberration	No data	–	Paton and Allison 1972
Human blood lymphocytes	Chromosomal aberration	No data	+	Shiraishi et al. 1972

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Table 3-11. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human blood lymphocytes	Chromosomal aberration	No data	–	Deknuddt and Deminatti 1978
Human blood lymphocytes	Chromosomal aberration	No data	±	Gasiorek and Bauchinger 1981
Human blood lymphocytes	DNA breaks	No data	+	Depault et al. 2006
Human lymphoblastoid cells	DNA breaks	No data	+	Mikhailova et al. 1997
Human fetal hepatic WRL-68 cells	DNA breaks	No data	+	Lopez-Ortal et al. 1999
Chinese hamster ovary CHO-K1 cells	DNA damage	No data	–	Misra et al. 1998
Rat L6 myoblast cells	DNA damage	No data	–	Misra et al. 1998
Rat Clone 9 liver cells	DNA damage	No data	–	Misra et al. 1998
Rat TRI 1215 liver cells	DNA damage	No data	–	Misra et al. 1998
Human blood lymphocytes	DNA damage	No data	+	Rozgaj et al. 2002
Human hepatoma cells (HepG2)	DNA damage	No data	+	Fatur et al. 2002
V79 Chinese hamster lung cells	DNA lesions	No data	+	Jianhua et al. 2006
Chinese hamster ovary CHO-K1 cells	DNA repair	No data	+	Lynn et al. 1997
Human 293T-Tet-Off-hMLH1 cells	DNA repair	No data	+	Lutzen et al. 2004
V79 Chinese hamster lung cells hprt locus	Gene mutation	No data	+	Jianhua et al. 2006
A _L human-hamster hybrid CD59 gene	Gene mutation	No data	+	Filipic and Hei 2004
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	±	Amacher and Paillet 1980
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	+	Oberly et al. 1982
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	+	+	Honma et al. 1999
Human blood lymphocytes	Micronuclei	No data	+	Migliore et al. 1999
Human blood lymphocytes (G ₀ phase)	Micronuclei	No data	–	Kasuba and Rozgaj 2002
Human blood lymphocytes (S phase)	Micronuclei	No data	+	Kasuba and Rozgaj 2002
Human diploid fibroblasts (MRC-5)	Micronuclei	No data	+	Seoane and Dulout 2001
Mouse spleen cells	Sister chromatid exchanges	No data	+	Fahmy and Aly 2000

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Table 3-11. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Bassendowska-Karska and Zawadzka-Kos 1987
Human blood lymphocytes (G ₀ phase)	Sister chromatid exchanges	No data	–	Saplakoglu and Iscan 1998
Human blood lymphocytes (S phase)	Sister chromatid exchanges	No data	+	Saplakoglu and Iscan 1998
Syrian hamster embryo cells	Transformation	No data	+	Casto et al. 1979
Rat ventral prostate cells	Transformation	No data	+	Terracio and Nachtigal 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	+	Denizeau and Marion 1989

– = negative result; + = positive result; ± = weakly positive; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

human cells have shown mixed results (Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Paton and Allison 1972; Shiraishi et al. 1972). For the most part, *in vitro* studies have not shown cadmium to induce SCE in human cells (Bassendowska-Karska and Zawadzka-Kos 1987; Saplakoglu and Iscan 1998). However, a study by Fahmy and Aly (2000) did observe SCE in mouse spleen cells following cadmium treatment. Kasuba and Rozgaj (2002) and Saplakoglu and Iscan (1998) evaluated the ability of cadmium to induce micronuclei and SCE in human lymphocytes *in vitro* respectively, at two different stages of the cell cycle, G₀ and S phase. These studies observed that the genotoxicity of cadmium may vary depending on the stage of the cell cycle as both micronuclei and SCE were induced in cells in S phase, but not in cells in G₀ phase. These observations may in part explain some of the contradictory findings regarding cadmium genotoxicity in the literature.

Positive mutagenicity results have been found in some studies using bacterial cells (Kanematsu et al. 1980; Mandel and Ryser 1984; Nishioka 1975; Wong 1988), in studies using yeast (Putrament et al. 1977; Schiestl et al. 1989), and in a single study using *Drosophila melanogaster* (Vasudev and Krishnamurthy 1979). Other studies report negative mutagenicity results in bacterial cells (Bruce and Heddle 1979; Milvy and Kay 1978) and in *D. melanogaster* (Inoue and Watanabe 1978; Ramel and Mangusson 1979).

3.4 TOXICOKINETICS

Cadmium metal and cadmium salts are not well absorbed; approximately 25, 1–10, or <1% of the dose is absorbed following inhalation, oral, or dermal exposure. Several factors can influence inhalation and oral absorption efficiency; for example, cadmium in cigarette smoke has a higher absorption efficiency due to its small particle size and cadmium absorption from the gastrointestinal tract is increased in individuals with poor iron status. Following absorption from any route of exposure, cadmium widely distributes throughout the body, with the highest concentrations found in the liver and kidney. Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. Absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal. Approximately 0.007 and 0.009% of the body burden is excreted in the urine and feces, respectively, per day.

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3.4.1 Absorption**3.4.1.1 Inhalation Exposure**

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine suspended particulate matter. When inhaled, some fraction of this particulate matter is deposited in the airways or the lungs, and the rest is exhaled. Large particles (greater than about 10 μm in diameter) tend to be deposited in the upper airway, while small particles (approximately 0.1 μm) tend to penetrate into the alveoli. While some soluble cadmium compounds (cadmium chloride and cadmium sulfate) may undergo limited absorption from particles deposited in the respiratory tree, the major site of absorption is the alveoli. Thus, particle size, which controls alveolar deposition, is a key determinant of cadmium absorption in the lung (Nordberg et al. 1985).

No direct data are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure (5–20% after 15 minutes to 2 hours) (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986) due to absorption of cadmium and lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in lung differs somewhat among chemical forms, but the pattern does not correlate with solubility (Glaser et al. 1986; Rusch et al. 1986).

Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorption of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985; Takenaka et al. 2004).

Based on the physiology of the human respiratory tree, a comprehensive model has been developed to predict the kinetics of inhaled cadmium in humans (Nordberg et al. 1985). Results of this model suggest that only about 5% of particles $>10 \mu\text{m}$ in diameter will be deposited, up to 50% of particles $<0.1 \mu\text{m}$ will be deposited, and between 50 and 100% of cadmium deposited in the alveoli will ultimately be absorbed (Nordberg et al. 1985).

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3.4.1.2 Oral Exposure

Most ingested cadmium passes through the gastrointestinal tract without being absorbed (Kjellström et al. 1978). Measurement of gastrointestinal absorption is complicated by the fact that not all of a dose initially retained in the gastrointestinal system can be considered to be absorbed, because some portion may be trapped in the intestinal mucosa without crossing into the blood or lymph (Foulkes 1984). Thus, measures of whole-body cadmium retention may overestimate cadmium absorption (at least in the short-term). On the other hand, some absorbed cadmium may be excreted in urine or feces, so that retention may underestimate exposure. However, this underestimate is probably minor because excretion of absorbed cadmium is very slow (see Section 3.4.4.2).

Cadmium absorption has been estimated based on the retention of cadmium in the bodies of humans following ingestion of radioactive cadmium. Estimated cadmium absorption ranged from 1.1 to 10.6% (Flanagan et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973; Shaikh and Smith 1980; Vanderpool and Reeves 2001). Although some studies have reported higher absorption levels (25–42%), this was based on cadmium retention measurements for 3–5 days after exposure that was probably too short to accurately measure cadmium transfer from the intestinal mucosa to circulation (Crews et al. 2000; Rahola et al. 1973). Using estimated cadmium intakes from national data and measured renal and urinary cadmium levels in healthy nonsmokers, cadmium absorption rates of 3–5% have been estimated (Ellis et al. 1979; Morgan and Sherlock 1984). In a balance study of women with high background cadmium intakes (mean urinary cadmium levels of 2.7–5.16 µg/g creatinine); the mean absorption rate in subjects examined for 7 days was 6.5% (Horiguchi et al. 2004).

The body store of iron influences cadmium absorption; subjects with low iron stores (assessed by serum ferritin levels) had an average absorption of 6 and 8.9%, while those with adequate iron stores had an average absorption of 2.3 and 2.4% (Flanagan et al. 1978; Shaikh and Smith 1980). Several epidemiology studies have found significant negative correlations between body iron (assessed via serum ferritin and/or transferrin levels) and cadmium body burden (blood cadmium and/or urinary cadmium levels) among men and women (Apinan et al. 2010) and among never-smoking, nonpregnant, non-menopausal women (Gallagher et al. 2011; Meltzer et al. 2010). Studies in rats have shown that iron deficiency results in the upregulation of divalent metal transporter 1 (DMT1) and metal transporter protein 1 (MTP1) in the duodenum, which may facilitate the absorption of cadmium (Kim et al. 2007; Ryu et al. 2004). Other epidemiology studies have found significantly higher cadmium body burdens in women with lower iron stores (Kippler et al. 2009). In contrast, a study of anemic females with high

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background cadmium levels did not find a significant alteration in cadmium absorption, as compared to healthy females; however, cadmium absorption was lower in the anemic group (13.6%) than in healthy group (27.4%) (Horiguchi et al. 2004). It is not known if the differences in the methods used to estimate cadmium absorption (kinetic study using radiolabelled cadmium versus a balance study) or the high background cadmium intake in the Horiguchi study resulted in the discrepancy between the two studies. There is some indication that not all forms of cadmium are equally absorbed. Some populations with high dietary-cadmium exposure from Bluff oysters (McKenzie-Parnell et al. 1988) or seal meat (Hansen et al. 1985) have been found not to have elevated blood-cadmium levels, perhaps due to the particular form of cadmium in these foods.

Crews et al. (2000) estimated that 42% of a cadmium dose incorporated into porridge was retained in the body 5 days after exposure (as measured by fecal excretion of radiolabelled cadmium); however, the fecal collection period was probably too short to accurately measure cadmium absorption. The investigators also attempted to measure cadmium absorption in 12-month-old infants; 18% of the labeled cadmium in the porridge was retained in the body after 4 days. As with the adult data, the collection period may have been too short to accurately measure cadmium absorption in the infants.

Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. In mice, 0.27–3.2% of an oral dose of cadmium chloride was retained after 3–5 days (Bhattacharyya et al. 1981; Engstrom and Nordberg 1979), and in rats, 2–3% of a single oral dose of cadmium chloride was retained (Moore et al. 1973; Schafer et al. 1990). Following 30 days of oral exposure, 0.2–0.3% of an administered dose was retained in rats (Muller et al. 1986). After 4 weeks of dietary exposure to cadmium, absorption of cadmium was reduced to one-third the absorption of rats without pre-exposure to cadmium (Schafer et al. 1990). Cadmium pigments (cadmium sulfide and cadmium sulfoselenide) appear to be absorbed much less than cadmium chloride in rats (ILZRO 1977). Increases in absorption have been observed during gestation and lactation, 0.37 and 0.35% of cadmium administered via gavage was absorbed in mice on gestation days 8 and 15 and 0.56, 0.60, and 0.30% on lactation days 10, 17, and 24, as compared to 0.27% in nonpregnant controls; absorption was only significantly different from nonpregnant controls on lactation days 10 and 17 (Bhattacharyya et al. 1981). Similar findings were observed in mice continuously exposed to cadmium during pregnancy and/or lactation (Bhattacharyya et al. 1982, 1986).

The absorption of cadmium from the gastrointestinal tract has been extensively studied in rats and mice, and a number of factors are recognized that influence absorption. Absorption appears to take place in two

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phases: uptake from lumen into mucosa, and transfer into the circulation (Foulkes 1985). Phase 1 may involve sequestering of cadmium by metallothionein (Foulkes 1980), but any protective effect is overloaded at moderate doses (Kotsonis and Klaassen 1978). Uptake behaves like a saturable process with fractional absorption decreasing at high concentrations (Foulkes 1980). There is evidence, however, to suggest that this saturation results from charge neutralization at the membrane (Foulkes 1985), so that it need not be assumed that there is a specific system for carrying cadmium into the body. At doses high enough to damage gastrointestinal mucosa, fractional absorption is increased (Andersen et al. 1988; Goon and Klaassen 1989; Lehman and Klaassen 1986). Cadmium bound to metallothionein was absorbed by rats to a lesser extent than cadmium added to the diet as cadmium chloride, but kidney cadmium content was only slightly less (Groten et al. 1990).

Maitani et al. (1984) compared the distribution of cadmium after oral administration of either cadmium ions or Cd-thionein in male CF-1 mice given 0.5 mg Cd/kg, per os (po), as cadmium chloride in saline, cadmium chloride in control rat liver homogenate, cadmium thionein in saline, Cd-TH in liver homogenate, or liver homogenate from Cd-treated rats. In all cases, 85–90% of the cadmium dose was present in feces within 24 hours. However, in groups receiving cadmium chloride, more cadmium was found in feces on days 2 and 3, compared to those receiving cadmium-thionein. In a companion study, tissue levels indicated that less cadmium was absorbed when rats received cadmium-thionein in saline than cadmium chloride in saline. Cadmium-thionein added to liver homogenate or liver homogenate containing cadmium-thionein increased the absorption of cadmium, resulting in renal cadmium levels similar to those in mice receiving cadmium chloride in saline. The kidney/liver cadmium concentration ratio (9) was the same for cadmium-thionein in all three media. Although Cd-TH gave much higher kidney/liver cadmium ratios than cadmium chloride (9 versus 2), renal cadmium concentrations were the same or lower than after cadmium chloride treatments. The authors concluded that the high kidney/liver cadmium ratio after cadmium-thionein treatment versus cadmium chloride was due to lower concentrations of cadmium in liver rather than marked increases in renal cadmium levels. While the chemical form of cadmium administered affects the absorption and distribution, the amount of cadmium reaching the kidney after cadmium-thionein administration is similar to that after cadmium chloride administration.

At moderate doses of cadmium, the presence of divalent and trivalent cations, such as calcium, chromium, magnesium, and zinc, may decrease cadmium uptake, probably by a nonspecific effect on the charge distribution of the intestinal brush border membrane (Foulkes 1985). However, the influence of cations on cadmium absorption is complex, because zinc can increase the amount of cadmium absorbed

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from the intestine (Jaeger 1990). A refined diet high in fat and protein increases cadmium absorption in mice, partially due to increased gastrointestinal passage time (Schafer et al. 1986). Studies in newborn rats and pigs also provide evidence that diet constituents influence cadmium absorption; absorption of cadmium chloride was higher when administered in water compared to cereal-based infant formula (Eklund et al. 2001, 2004). Diets low in iron increase cadmium absorption (Flanagan et al. 1978; Reeves and Chaney 2001, 2002; Schafer et al. 1990); a diet low in calcium will also increase cadmium absorption (Reeves and Chaney 2001, 2002). In contrast, low levels of dietary iron did not increase cadmium absorption in suckling piglets; however, iron supplementation did increase cadmium absorption (Öhrvik et al. 2007); this difference may be due to the high cadmium dose used in the study. Zinc deficiency may result in an increased accumulation of cadmium in the intestinal wall, but does not affect transport into the blood (Foulkes and Voner 1981; Hoadley and Cousins 1985). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs. Thus, for a given individual, the absorption following oral exposure to cadmium is likely to depend on physiologic status (age; body stores of iron, calcium, and zinc; pregnancy history; etc.) and, also, on the presence and levels of ions and other dietary components ingested with the cadmium.

3.4.1.3 Dermal Exposure

A few measurements of dermal absorption of cadmium in animals have been made, with only one *in vitro* study using human skin to determine the percutaneous absorption of cadmium.

A study by Wester et al. (1992) evaluated the percutaneous absorption of cadmium from water and soil into and through human skin using *in vitro* skin cells. Radioactive cadmium ($^{109}\text{cadmium}$ chloride) was made to a concentration of 116 ppb in water or 13 ppb in filtered soil (26% sand, 26% clay, 48% silt, 0.9% organic content). Cadmium chloride was administered either at 5 $\mu\text{L}/\text{cm}^2$ or 2 volumes of 2.5 $\mu\text{L}/\text{cm}^2$ (the same amount of cadmium apparently applied). Human cadaver skin dermatomed at 500 μm was placed in flow-through skin cells and perfused with human plasma. Approximately 0.1–0.6% of the cadmium chloride in water entered the plasma perfusate over the 16-hour perfusion period, while 2.4–12.7% of applied dose remained in the skin. Most of the cadmium (74–93%) remained unabsorbed and was recovered from the skin surface. Total recoveries ranged from 88 ± 20 to 103 ± 3 . When cadmium-contaminated soil (13 ppb cadmium chloride) was applied to the skin surface, plasma levels ranged from 0.02 to 0.07% of the applied dose, while the skin contained 0.06–0.13% of applied

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dose. Surface wash ranged from 82 to 102% of applied dose. Total recoveries were from 83 ± 33 to 106 ± 2 . The large differences between water and soil absorption into the plasma and retention in the skin were attributed to differences in cadmium partition coefficients, measured to be 3.61×10^1 for stratum corneum (powdered):water and 1.03×10^5 for soil:water. These measurements indicate that soil has a relatively higher affinity for cadmium than does the stratum corneum. The transfer of cadmium from soil to skin depends on the soil's binding capacity and water retention and variables describing the physical contact with the skin. When cadmium levels in the soil were increased from 6.5 to 65 ppb, skin levels correspondingly increased, but plasma receptor fluid levels remained constant. This suggests that, with *in vitro* perfusion, the surface concentration of cadmium will influence skin cadmium concentration, but that absorption into plasma receptor fluid is relatively independent of the skin surface concentration. The authors offer the caveat that *in vitro* methods can influence results and therefore, the receptor fluid accumulation must be interpreted with caution. The authors calculate that a whole-body exposure to cadmium at 116 ppb in water with 0.5% absorption will result in a daily systemic intake of about 10 μg cadmium.

A few animal studies are available that describe the percutaneous absorption of cadmium as estimated from the accumulation of cadmium in the liver and kidneys of mice and rabbits. Male rabbits (strain not specified) dosed with cadmium chloride percutaneously via a 1% aqueous solution (6.1 mg cadmium) or 2% ointment (12.2 mg cadmium) over a 10-cm² shaved area (Kimura and Otaki 1972). Animals were treated 5 times over 3 weeks (duration of exposure not reported) and were killed 2 weeks after the last application. Only cadmium contents of liver and kidney were measured, so total absorption through the skin may have been greater. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.4–0.61% 2 weeks after the end of cadmium exposure. This percentage was similar for aqueous solution or hydrocarbon ointment. Similarly, male hairless mice (strain not specified) were dosed with cadmium chloride percutaneously with a 2% ointment (containing 0.61 mg cadmium) 1 or 5 times in a week (duration of exposure not reported) and killed 1 week later (Kimura and Otaki 1972). Accumulated amounts of cadmium in the liver and kidneys were found to be 0.2–0.87%.

Cadmium was detected in liver, kidneys, and urine following dermal exposure in guinea pigs (Skog and Wahlberg 1964). The disappearance of cadmium from cadmium chloride in water applied to guinea pig skin was dependent on concentration, with a peak mean absorption of 1.8% over 5 hours at 0.239 molar cadmium (about a 2.7% solution). Less absorption occurred both at higher and lower concentrations of a cadmium chloride solution applied to the skin (Skog and Wahlberg 1964).

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The results from all of these studies suggest that dermal absorption is slow, and would be of concern only in situations where concentrated solutions would be in contact with the skin for several hours or longer.

3.4.2 Distribution

Cadmium is widely distributed in the body, with the major portion of the body burden located in the liver and kidney. Animals and humans appear to have a similar pattern of distribution that is relatively independent of route of exposure, but somewhat dependent on duration of exposure.

3.4.2.1 Inhalation Exposure

Cadmium was found in autopsy samples from nearly all organs of a worker extensively exposed to cadmium dust, with greatest concentrations in the liver, kidney, pancreas, and vertebrae (Friberg 1950). In workers dying from inhalation of cadmium, lung-cadmium concentration was somewhat lower than liver or kidney cadmium concentration (Beton et al. 1966; Lucas et al. 1980; Patwardhan and Finckh 1976). The concentration of cadmium in the liver of occupationally exposed workers generally increases in proportion to intensity and duration of exposure to values up to 100 µg/g (Gompertz et al. 1983; Roels et al. 1981b). The concentration of cadmium in the kidney rises more slowly than in the liver after exposure (Gompertz et al. 1983) and begins to decline after the onset of renal damage at a critical concentration of 160–285 µg/g (Roels et al. 1981b).

In animals acutely exposed to cadmium carbonate aerosols, about 60% of the inhaled dose is found in the gastrointestinal tract, transported by mucociliary clearance (Moore et al. 1973). Following a 2-hour inhalation of approximately 100 mg/m³ of cadmium, cadmium concentration in rat liver increased from an initial concentration of 0.8 µg/g in males and 1.9 µg/g in females immediately after exposure up to a peak of about 2 µg/g in males and 3.8 µg/g in females 1 week postexposure, then declined to 1.7 and 2.5 µg/g, respectively, by 30 days postexposure. The kidney concentrations were initially <0.5 µg/g in males and females, rising to approximately 8 µg/g in both sexes by 1 week postexposure and to 18 µg/g in males and 15 µg/g in females by 30 days postexposure (Rusch et al. 1986).

3.4.2.2 Oral Exposure

As discussed in Chapter 6, most nonoccupationally exposed people are exposed to cadmium primarily through the diet. Cadmium can be detected in virtually all tissues in adults from industrialized countries, with greatest concentrations in the liver and kidney (Chung et al. 1986; Sumino et al. 1975). Average

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cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40–50 µg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). Liver cadmium concentrations also begin near zero at birth, increase to typical values of 1–2 µg/g wet weight by age 20–25, then increase only slightly thereafter (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984; Sumino et al. 1975).

Distribution of cadmium in animals after oral exposure is similar to that found in humans, with highest accumulation in the liver and kidneys, and lower levels spread throughout the rest of the body (Kotsonis and Klaassen 1978; Weigel et al. 1984). Liver and kidney cadmium concentrations are comparable after short-term exposure (Andersen et al. 1988; Jonah and Bhattacharyya 1989), but the kidney concentration exceeds the liver concentration following prolonged exposure (Kotsonis and Klaassen 1978), except at very high exposures (Ando et al. 1998; Bernard et al. 1980; Hiratsuka et al. 1999). In mice orally exposed to cadmium during lactation, 53% of the whole-body cadmium was found in the kidneys as compared to 27% in nonpregnant controls (Bhattacharyya et al. 1982).

Maitani et al. (1984) compared the distribution of cadmium in rats after an acute oral administration of either cadmium ions or cadmium bound to metallothionein. In all cases, 85–90% of the dose was present in the feces within 24 hours postexposure. More of the cadmium-thionein was retained after 2–3 days, and less of the cadmium-thionein was distributed to the liver than was the case for the ionic cadmium. Kidney levels were comparable.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sorell and Graziano 1990). Thus, timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies.

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Goyer and Cherian (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Cadmium levels in human milk are 5–10% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987). Bhattacharyya et al. (1982) examined the maternal transfer of cadmium to pups during gestation and lactation in mice. Approximately 3, 11, and 25% of maternal cadmium was transferred to the pups following gestation-only exposure, lactation-only exposure, and gestation and lactation exposure, respectively.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to cadmium. Elevated levels of cadmium were found in the liver and kidneys of rabbits and mice dermally exposed to cadmium (Kimura and Otaki 1972).

3.4.3 Metabolism

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion does bind to anionic groups (especially sulfhydryl groups) in proteins (especially albumin and metallothionein) and other molecules (Nordberg et al. 1985). Plasma cadmium circulates primarily bound to metallothionein, and albumin (Foulkes and Blanck 1990; Roberts and Clark 1988).

3.4.4 Elimination and Excretion

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is not absorbed and is excreted in the feces. Absorbed cadmium is excreted very slowly, with urinary and fecal

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excretion being approximately equal (Kjellström and Nordberg 1978). The half-time for cadmium in the whole body in humans was >26 years (Shaikh and Smith 1980) and half-times of several months up to several years have been calculated in mice, rats, rabbits, and monkeys (Kjellström and Nordberg 1985). Half-times in the slowest phase were from 20 to 50% of the maximum life span of the animal (Kjellström and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellström and Nordberg (1985) developed a range of half-times from their kinetic model of 6–38 years for the human kidney and 4–19 years for the human liver.

3.4.4.1 Inhalation Exposure

Cadmium excretion in urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion markedly increases (Roels et al. 1981b). Fecal excretion in workers occupationally exposed to cadmium reflects mainly cadmium dust swallowed from industrial air and/or incidentally ingested from contaminated hands (Adamsson et al. 1979).

In rats, following a 2-hour inhalation exposure to cadmium carbonate, cadmium was primarily eliminated in the feces, with a minor component (approximately 1% of fecal excretion) in the urine (Rusch et al. 1986). Cadmium excretion by both routes declined with time after exposure, with significantly elevated excretion found at 7 days, but not 30 days, after exposure (Rusch et al. 1986). Most of the cadmium initially excreted in the feces was probably not absorbed, but rather represented particles transported from the lung to the gastrointestinal tract (Moore et al. 1973).

3.4.4.2 Oral Exposure

Following oral exposure, the major proportion of administered cadmium is found in the feces, because absorption is so low (see Section 3.4.1.2) (Kjellström et al. 1978). Among five healthy adult volunteers, fecal excretion of a single dose of radiolabeled cadmium declined with time up to 45 days after ingestion, while urinary excretion remained at a low, near-constant level (Rahola et al. 1973). After about 20 days, fecal and urinary excretion appeared to be comparable (Rahola et al. 1973). In contrast, among four healthy adults ingesting cadmium in intrinsically labeled crabmeat, fecal excretion was 30 times higher than urinary excretion up to 10 weeks after ingestion of the test meal (Newton et al. 1984). In rats orally exposed to up to 0.35 mg/kg/day of cadmium in the diet for 60 days, no significant increase in

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urinary cadmium content was found (Weigel et al. 1984). The overall excretion of absorbed cadmium is slow, with biological half-times of 70–270 days in rats or mice orally exposed to cadmium (Engstrom and Nordberg 1979; Moore et al. 1973).

In a comprehensive model developed for human cadmium toxicokinetics, parameters for urinary and fecal excretion were derived by adjustments to empirical data derived from human and animal studies (Kjellström and Nordberg 1978, 1985). Fecal excretion constitutes unabsorbed cadmium plus "true" excretion originating from blood via the intestinal wall (a function of cadmium body burden) and from bile via the liver (a function of cadmium liver burden) (Kjellström and Nordberg 1985). Urinary excretion depends on blood concentration and kidney concentration, and total excretion is assumed to equal daily intake at steady state. Using these methods and assumptions, daily fecal and urinary excretion is estimated to be 0.007 and 0.009% of body burden, respectively (Kjellström and Nordberg 1978, 1985). A whole-body retention half-time estimate of >26 years was obtained by Shaikh and Smith (1980) in a study using orally ingested radiolabelled cadmium and monitoring a subject for over 2 years.

Groups of 10 female outbred albino rats were exposed to cadmium in drinking water (as cadmium chloride) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, at 3 weeks of gestation, or 3 weeks into lactation). After weaning, exposure to cadmium was terminated. In dams, kidney concentrations exceeded liver concentrations, while in pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11–21). The concentrations in the dams were several orders higher than in the offspring. After discontinuation of exposure, organ concentration slightly decreased in dams (2% in liver and 12% in kidneys), while in pups, the decrease was 84% in the liver and 62% in the kidneys. These values do not indicate cadmium elimination but rather dilution caused by growth (Kostial et al. 1993).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cadmium. Cadmium was reportedly detected in urine in guinea pigs dermally exposed to aqueous cadmium chloride, but no details are available (Skog and Wahlberg 1964).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987a). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species.

Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for cadmium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

3.4.5.1 Summary of Cadmium PBPK Models

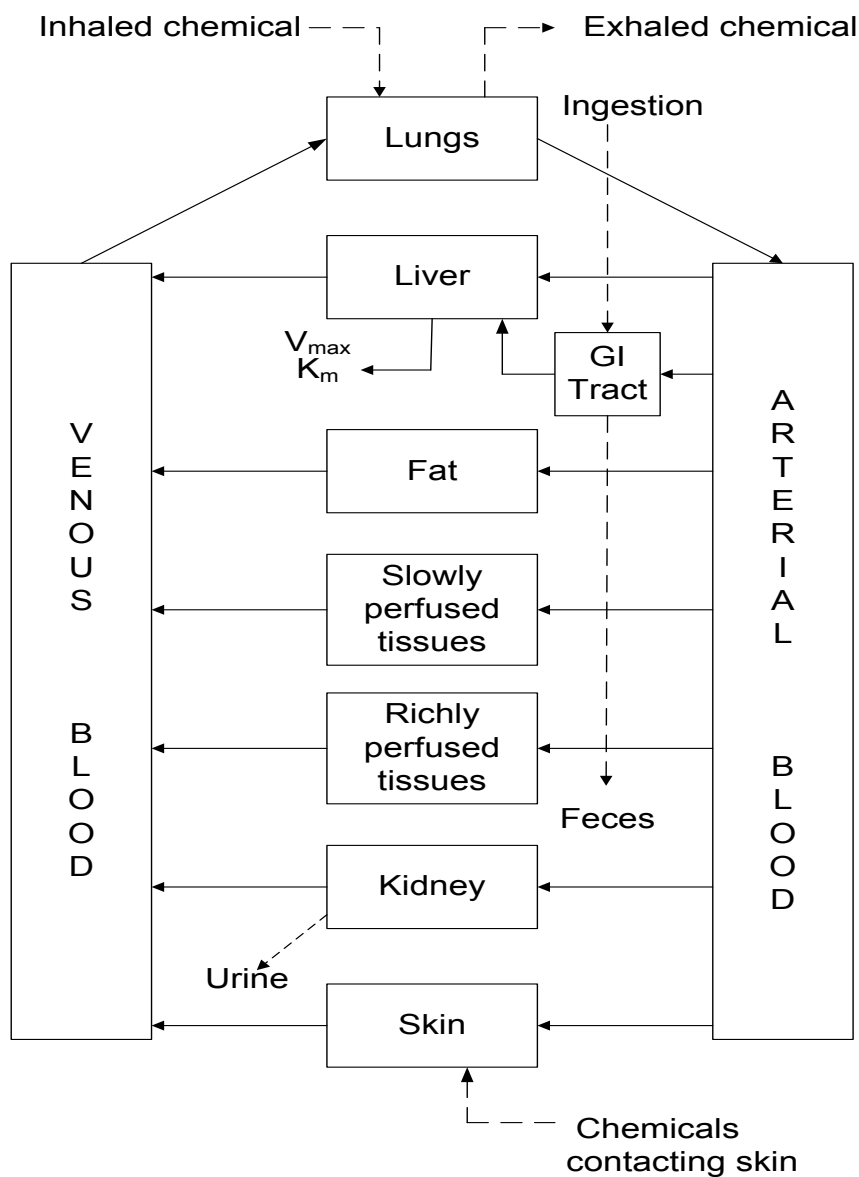
Several models have been reported to describe the kinetics of cadmium in mammalian systems. Of these models, the Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) has been the most widely used for cadmium risk assessment. Three of the most relevant cadmium models will be discussed here.

3.4.5.2 Cadmium PBPK Model Comparison

Although the Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) has its limitations, it provides the best overall description of cadmium toxicokinetics and is largely based on human data. The Shank (Shank et al. 1977) and Matsubara-Khan (Matsubara-Khan 1974) models are not as useful for human risk assessment applications, but they do provide useful insights into the absorption, distribution, and compartmentalization of cadmium in laboratory animals. These insights may have some future use in human risk assessment as PBPK models for cadmium continue to be refined.

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Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

3.4.5.3 Discussion of Cadmium Models

The Nordberg-Kjellström Model

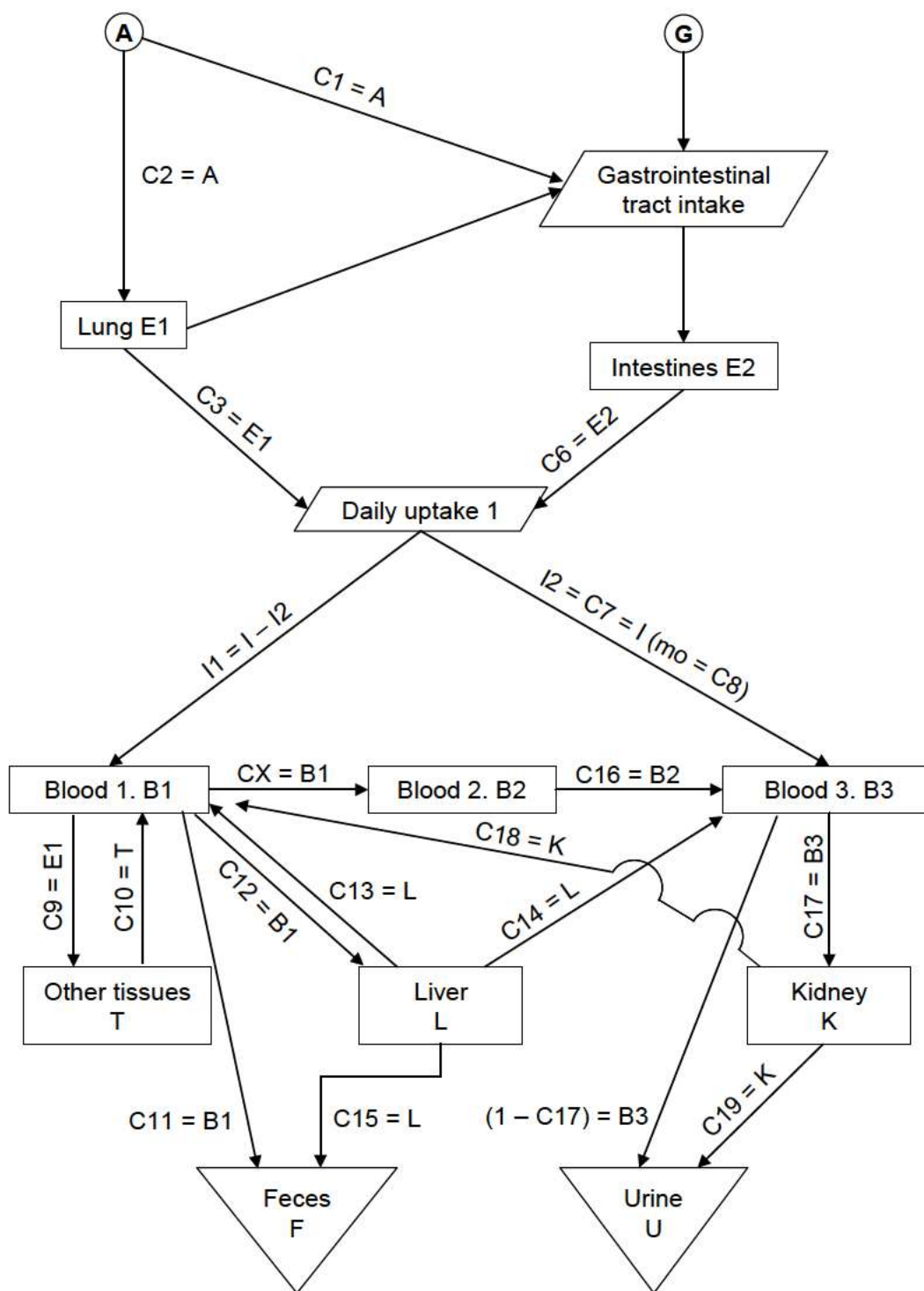
The Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) is a linear multicompartment model that is the most commonly used model for cadmium risk assessment work today. The Nordberg-Kjellström schematic model diagram is shown in [Figure 3-4](#).

Risk assessment. The Nordberg-Kjellström model has been demonstrated to be a useful model in human risk assessment work. Frazier (1994), however, noted that the model has two major limitations: (1) the linear nature of the model may not adequately allow a good description of known nonlinearities in biological responses to cadmium dosing, and (2) the phenomenological approach taken with this model does not provide a foundation for incorporating biological variability into the model parameters.

Description of the Model. The Nordberg-Kjellström model (see [Figure 3-4](#)) is a linear multi-compartment model that describes the disposition of cadmium via the oral and inhalation routes of exposure only. Dermal exposure and subsequent absorption through the skin were assumed to be negligible in this model. For inhalation exposures, the model accounts for different deposition patterns for different size particles in nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract. Particles with mass median aerodynamic diameter (MMAD) of 5 μm (i.e., cadmium-laden dust) were assumed to distribute mainly to the nasopharyngeal region (75%), with lesser amounts depositing in the alveolar (20%) and tracheobronchial (5%) regions. Particles of 0.05 μm MMAD (i.e., cigarette smoke) were assumed to deposit 50% in the alveolar compartment, 10% in the tracheobronchial compartment, and none in the nasopharyngeal compartment. The remaining amounts are exhaled. For all particle sizes initially deposited in the nasopharyngeal and tracheobronchial compartments, mucociliary clearance clears some particles from the respiratory tract to enter the oral compartment for absorption or out of the body and back to the environment. Assumed model coefficient values and the available physiological parameters are shown in [Table 3-12](#).

For the oral route of exposure, cadmium may enter the gastrointestinal tract via food or water contaminated with cadmium, or as cadmium particles embedded in mucus from the respiratory tract via the mucociliary/tracheobronchial escalator. By either route of exposure, the model assumes that cadmium enters into any of three blood compartments (B) (see [Figure 3-4](#)). B1 is the plasma compartment where

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Figure 3-4. A Schematic Representation of the Nordberg-Kjellström Model

Source: Kjellström and Nordberg 1978

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Table 3-12. Assumed Model Parameters and Some Physiologic Parameters for the Nordberg-Kjellström Model

Coefficient or parameter	Assumed range	Unit ^a	Values fitting to empirical data
Model parameters			
C1	0.1–0.2 (cigarette smoke)		0.1
	0.4–0.9 (factory smoke)		0.7
C2	0.4–0.6 (cigarette smoke)		0.4
	0.1–0.3 (factory smoke)		0.13
C3	0.01–1.0	day ⁻¹	0.05
C4	0.1xC3 = 0.001–0.1	day ⁻¹	0.005
C5	0.03–0.1		0.048
C6	0.05	day ⁻¹	0.05
C7	0.2–0.4		0.25
C8	0.5–5.0	µg	1
C9	0.4–0.8		0.44
C10	0.00004–0.0002	day ⁻¹	0.00014
C11	0.05–0.5		0.27
C12	0.1–0.4		0.25
C13	0–0.0001	day ⁻¹	0.00003
C14	0.0001–0.0003	day ⁻¹	0.00016
C15	0–0.0001	day ⁻¹	0.00005
C16	0.004–0.015	day ⁻¹	0.012
C17	0.8–0.98		0.95
C18	0–0.0001	day ⁻¹	0.00001
C19	0.00002–0.0002	day ⁻¹	0.00014
CX	0.01–0.05		0.04
C20	0.05–0.5		0.1
C21	0–0.000002	day ⁻¹	0.0000011
Physiologic parameters			
Average liver weight	1,500	gram	
Average blood volume	70	mL/kg	
Average blood specific gravity	1.06		
Average daily urine excretion (adult)	1.0	L	
Average daily urine excretion (aged)	0.9	L	
Average daily urine excretion (child)	0.5	L	

^aBlanks indicate a unitless value.

Source: Kjellström and Nordberg 1978; Nordberg and Kjellström 1979

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cadmium may bind to plasma components (i.e., albumin and other organic constituents). B2 is the red-blood cell compartment, which represents the accumulation of cadmium in erythrocytes, while B3 represents the binding of cadmium to metallothionein. The model does not take into account induction of metallothionein after cadmium exposure. From the blood, cadmium is calculated to distribute to either the liver, kidney, or "other tissues," the major accumulation sites. Elimination is either via the feces or in the urine. The transport of cadmium between the compartments is assumed to follow first-order exponential functions and is driven on concentration-dependent gradients.

Validation of the model. The Nordberg-Kjellström model was validated using several independent sets of human data from both Sweden and Japan. The data set by Friberg et al. (1974) estimated that smoking 20 cigarettes a day would result in an inhalation of 2–4 $\mu\text{g/day}$ of cadmium, assuming smoking started at 20 years of age and daily cadmium intake from food was 16 $\mu\text{g/day}$. Based on the Friberg et al. (1974) data, the model predictions of cadmium concentrations in the kidney agreed well with the observed data from a study by Elinder et al. (1978); however, the model predicted higher than expected values for liver cadmium compared to the observed data from the Elinder study. The model's urinary excretion of cadmium (0.84 $\mu\text{g/24 hours}$ for a 50-year-old person) agreed well with the observed data (0.56–0.8 $\mu\text{g/24 hours}$). The model predicted blood cadmium levels for Swedish smokers to be about 2 ng/g which compared well to the actual concentration of 1.6 ng/g .

The model was also validated against a data set for an average 45-year-old Japanese person living in Tokyo whose daily intake of cadmium is 40 μg via food and 2.7 μg via the inhalation route. Subjects were assumed to be smokers averaging 24 cigarettes a day starting at age 20. Based on these exposure conditions, the measured values for cadmium in the kidney, liver, and "other tissues" (in this case, muscle only) were reported to be 65, 3.4, and 0.2 $\mu\text{g/g}$, respectively, with the model predicting 48, 3.2, and 0.18 $\mu\text{g/g}$. For blood and urine, the measured values were 4.5 $\mu\text{g/g}$ for blood and 1.1 $\mu\text{g/L}$ for urine; the model predicted 3.4 $\mu\text{g/g}$ and 1.3 $\mu\text{g/24 hours}$ (assuming 1 L of urine output/day, the value would be 1.3 $\mu\text{g/L}$).

Another study of Japanese people reported cadmium concentrations in urine in relation to high cadmium concentrations in rice in their daily diet. For people who consumed rice containing 0.04 $\mu\text{g/g}$ of rice (240 $\mu\text{g/day}$), the observed urinary level of cadmium was 7 $\mu\text{g/L}$; consumption of rice containing 1.1 $\mu\text{g cadmium/g}$ of rice (660 $\mu\text{g/day}$), resulted in an observed value of 14 $\mu\text{g/L}$ of urine. After making certain assumptions about the average daily consumption of rice containing an assumed amount of cadmium, and

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assuming an average urine production of 1 L/day, the model calculated urinary levels of 4.8 and 15.5 µg/L of urine, agreeing well with the observed values.

The model was also validated against a data set with high concentrations of cadmium in air (50 µg/m³) (Piscator 1972) and blood cadmium concentrations ranging from 10 to 50 ng/g whole blood. Calculated blood, urine, liver, and kidney levels of cadmium agreed only roughly with the observed values; however, the authors concluded that the model predictions may not be accurate based on the observations that workers with long exposure histories had most likely experienced higher exposure levels in the past, skewing the data set, resulting in poor model predictions. Another data set by Piscator (1984) involved a group of Swedish workers involved in polishing cadmium-plated objects, who were exposed to high concentrations of cadmium for ≤2 years. Cadmium levels were measured in the urine and blood. When this exposure data set was input into the model, the model could not adequately predict blood and urine levels for these workers.

Target tissues. The Nordberg-Kjellström model assumes that the kidney and liver are the two specific target tissues in which cadmium accumulates. The model also accounts for all other tissue accumulation in the "other tissues" compartment (i.e., muscle). The model assumes a human liver tissue half-life ($t_{1/2}$) of 4–19 years and a kidney $t_{1/2}$ of 6–38 years. For the "other tissue" compartments, $t_{1/2}$ was assumed to be 9–47 years. The Nordberg-Kjellström model does account for the loss of renal tubular epithelial cells leading to a loss of tubular reabsorptive capacity. This loss of cells could conceivably result in an increase in the excretion of cadmium from the tubules and an increase in the transport of cadmium from the tubules to the blood. This loss of cells is theorized to account for the large $t_{1/2}$ range for cadmium in the kidney. The model assumed that no changes in the movement of cadmium from the kidney to blood occurred with age and that the loss of cadmium from the kidney to the urine increased linearly after the age of 30.

The Nordberg-Kjellström model also accounted for differences in kidney and liver weights among different age groups and between peoples of different ethnic origins. The model corrected for differences in liver, kidney, blood, and "other tissue" weights with relation to age (1 and 79 years of age) and ethnicity (Japan and Sweden).

Species extrapolation. The Nordberg-Kjellström model was based solely on data collected from humans and was intended for human risk assessment applications. The model did not address any potential application for this model of cadmium in laboratory animals.

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High-low dose extrapolation. The Nordberg-Kjellström model has been shown to adequately predict fluid and tissue concentrations via the oral and inhalation routes of exposure for humans exposed to low doses of cadmium. However, the model has difficulty in adequately predicting fluid and tissue concentrations in humans exposed to high concentrations of cadmium, especially for those individuals exposed to high concentrations via the inhalation route.

Interroute extrapolation. The Nordberg-Kjellström model adequately predicted the fate of cadmium in target tissues after exposure via the inhalation and oral routes. The dermal route of exposure was not incorporated into the model parameters and was considered an insignificant route of exposure in humans.

The Shank Model

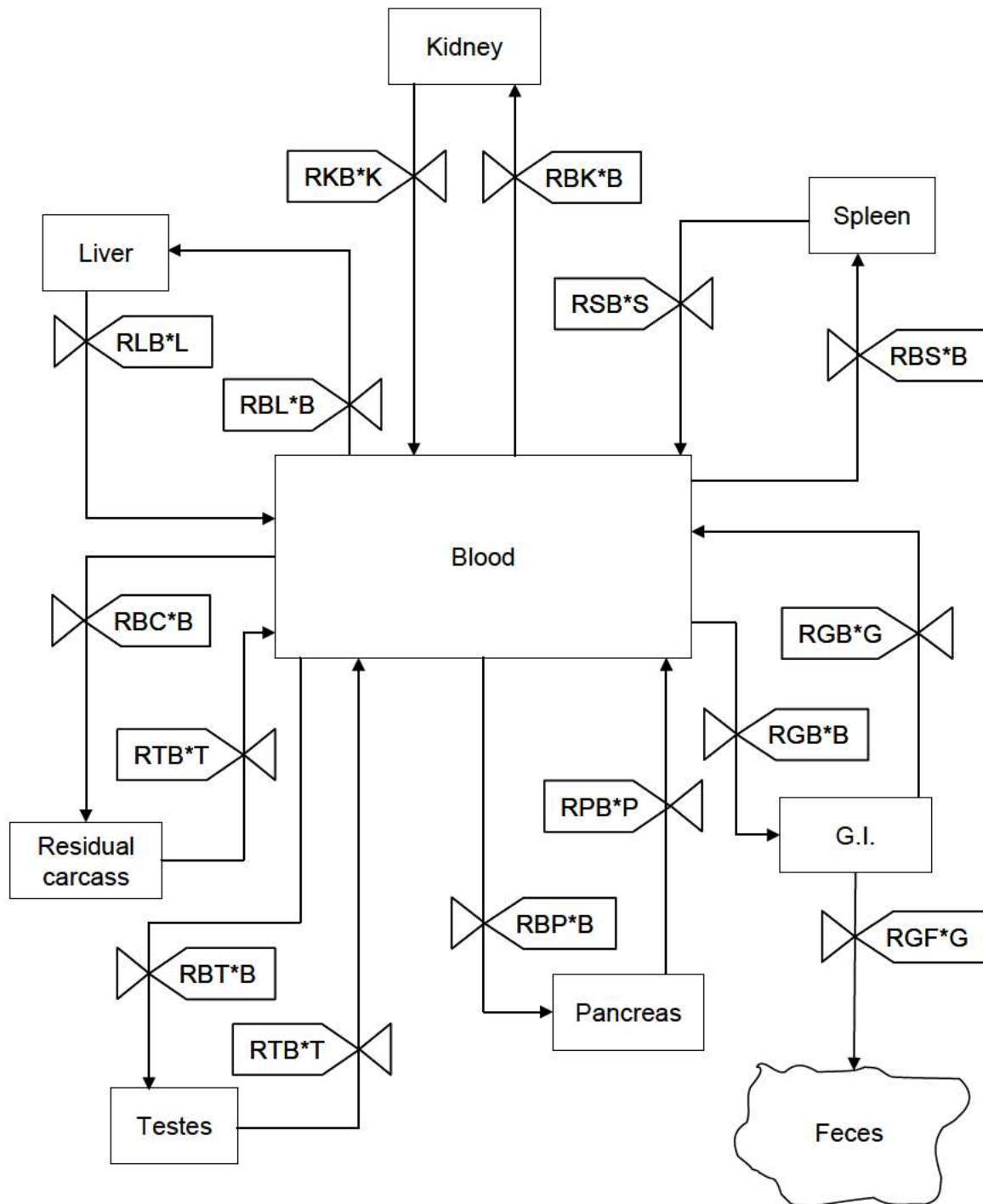
Risk assessment. The Shank model (Shank et al. 1977) may have the potential to serve as an alternative mathematical model for predicting the retention of cadmium in biological systems. Unfortunately, no human data were used to validate the Shank model for use as a risk assessment tool in cases of human exposure. In addition, the Shank model was validated only for the intravenous and subcutaneous routes of exposure; no data were presented for the oral, inhalation, or dermal routes of exposure.

Description of the model. A schematic representation of the Shank model is illustrated in [Figure 3-5](#). The model mathematically represents the dynamic transport of cadmium between compartments in a mammalian biological system based on the male adult SW/NIH mouse as the test animal species. The intent was to predict the retention of cadmium in other species of animals (including humans) without requiring an adjustment of species-specific rate constants from within the model.

Male adult mice of the SW/NIH strain were dosed intravenously with ^{109}Cd as ^{109}Cd acetate. Mice received 1–3 intravenous injections spaced 48 hours apart. Animals in each group were sacrificed at 2 and 10 minutes and 1, 10, and 48 hours after the last dose. Tissues (liver, kidney, pancreas, spleen, gastrointestinal tract, testes, carcass, and feces) were harvested and the radioactivity recorded. A nine-compartment model was derived. Cadmium kinetics between compartments are described by first-order kinetics. The individual compartment retention values, obtained from the distribution study, were incorporated into the model equations and the rate constants derived.

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Figure 3-5. A Schematic Representation of the Shank Model



Source: Forrester 1968

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Validation of the model. The Shank model was validated using three independent data sets. Mann (1973) dosed dogs, goats, and sheep with one intravenous injection of ^{109}Cd acetate (30 μCi), and the liver and kidneys were examined for cadmium content 8 weeks after administration. The Shank model's predicted values of cadmium retention in liver and kidneys at 8 weeks after a single administration were in good agreement with the observed values of the Mann (1973) study in all three species. Only data from the liver and kidneys were available for evaluation. A data set from a study by Gunn et al. (1968b) was used to evaluate the ability of the Shank model to predict the retention of cadmium in liver and kidney after a single subcutaneous administration of cadmium chloride. Animals in that study were sacrificed 2 weeks after administration, and the liver and kidneys were examined for cadmium content. The model values for the same time period were in very close agreement with observed values. Again, only data from the liver and kidneys were available for evaluation. Finally, a data set by Shanbaky (1973) was used to test the model's validity with multiple injections of cadmium acetate in rats. Five injections of cadmium acetate were administered over a 48-hour period; liver, kidneys, pancreas, spleen, and gastrointestinal tract were examined for cadmium content. The Shank model was found to be in close agreement with the arithmetic means of observed values found in the Shanbaky (1973) study.

No human data were presented to validate the model's effectiveness in predicting the cadmium retention in human target tissues after either a single or multiple dosing regime.

Target tissues. The target tissues for this model included the liver, kidney, pancreas, spleen, gastrointestinal tract, testes, and carcass of laboratory animals. No human tissue was used to derive cadmium retention in any of these tissues.

Species extrapolation. The model used goats, dogs, rats, mice, and sheep with various doses and dosing schemes of cadmium acetate and cadmium chloride and was found to serve as a good predictor of cadmium retention in the target tissues listed above. No human data were presented to determine if the model could satisfactorily predict the cadmium retention in human target tissues.

High-low dose extrapolation. High- and low-dose extrapolation was not specifically addressed by the Shank model.

Interroute extrapolation. Interroute extrapolations were addressed in a limited fashion by the Shank model. The model appeared to adequately predict the amount of cadmium retention in the target organs

of laboratory animals, in particular the liver and kidney, when dosed by either the intravenous or subcutaneous routes. The inhalation and dermal routes of exposure, and other parenteral routes of exposure (intramuscular, intraperitoneal, intradermal, etc.) were not addressed by the Shank model. No human data were presented to determine if interroute extrapolations were valid.

The Matsubara-Khan Model

Risk assessment. The Matsubara-Khan model (Matsubara-Khan 1974) has not been used as a tool in risk assessment for humans. This model does demonstrate that cadmium kinetics and biological half-lives vary by tissue.

Description of the model. The Matsubara-Khan model is a simple model that attempted to fit cadmium elimination kinetic parameters into either a one- or two-compartment model. To obtain the data for the model, male and female ICR mice (8 weeks of age) were administered a single subcutaneous injection of a known amount of ^{109}Cd chloride. Specific groups of mice were sacrificed at 1, 2, 4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents were removed and the amount of ^{109}Cd remaining in these tissues was determined.

An oral study was conducted in conjunction with the subcutaneous study described above. In the oral study, 8-week-old male mice (ddd x BALB/c; F₁) were orally administered $^{115\text{m}}\text{Cd}$ chloride by gavage. Groups of mice were sacrificed at 1, 2, 4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, liver, kidney, salivary gland, stomach wall, gonad, and spleen were removed and the amount of $^{115\text{m}}\text{Cd}$ remaining in these tissues was determined.

The rate of uptake, rate constants, and biological half-lives determined for the subcutaneous and orally dosed mice are summarized in [Table 3-13](#). Matsubara-Khan found that tissue kinetics in mice dosed subcutaneously with ^{109}Cd chloride fit into either a one- or two-compartment model, depending on the tissue. The data from the digestive tract organs (stomach wall, small intestine, and colon) were best fitted into a 1-compartment model, with a strained fit of the data from the digestive tract contents (stomach, small intestine, and colon contents) to the one-compartment model. Data from the blood, liver, kidneys, and salivary glands were best fitted to the two-compartment model. Extremely small second-rate constants in the kidneys and salivary glands indicate that the elimination of cadmium from these tissues is

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Table 3-13. Estimated Parameters, Rate of Uptake, Rate Constants, and Biological Half-Lives in Selected Mouse Organs After Subcutaneous and Oral Administrations of $^{109}\text{CdCl}_2$

Organ	Rate of uptake (95% CL)		Rate constants b and c (95% CL)		Biological half-life (days)	
	SC	PO	SC	PO	SC	PO
Liver	21	8.7	0.011 0.57	0.016 0.91	631.2	430.76
Kidney	22	1.4	0.0007 0.30	0.016 0.30	9902.3	4332.3
Salivary gland	21	0.33	0.0016 0.73	0.0047 0.78	4330.95	1500.89
Blood	0.15	NM	0.024 0.65	NM	291.1	NM
Stomach wall	1.7	0.36	0.0073	0.017	95	41
Stomach contents	0.68	NM	0.062	NM	11	NM
Small intestine	0.95	NM	0.01	NM	69	NM
Small intestine contents	2.5	NM	0.067	NM	10	NM
Colon	1.4	NM	0.013	NM	53	NM
Colon contents	4.1	NM	0.15	NM	4.6	NM
Gonad	NM	0.37	NM	0.012	NM	58
Spleen	NM	0.44	NM	0.0011	NM	630

CL = confidence limits; PO = oral; SC = subcutaneous; NM = not measured

Source: Matsubara-Khan 1974

very slow. For the oral study, similar findings were observed, with data from the gonads and spleen fitting the one-compartment model best. Biological half-lives were invariably longer for the subcutaneously dosed animals, while the rate constants were slightly smaller for the subcutaneously dosed animals. Sex-related differences in rate of uptake, rate constants, and biological half-lives were not found, except in the kidney data in which females had slightly smaller rate constants.

Validation of the model. No independent data sets were used to validate the Matsubara-Khan model.

Target tissues. For the subcutaneous injection study, the Matsubara-Khan model used blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents. For the oral study, the model used liver, kidney, salivary glands, stomach wall, gonads, and spleen.

Species extrapolation. No species extrapolations were performed in the Matsubara-Khan model.

High-low dose extrapolation. No high-low dose extrapolations were performed in the Matsubara-Khan model.

Interroute extrapolation. The Matsubara-Khan model compared the oral and subcutaneous routes and reported similar rate constants for many of the tissues examined. Biological half-lives varied considerably for the kidney and salivary gland, but were not much different for liver between the two routes of exposure.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Cadmium can be absorbed by the inhalation, oral, and dermal routes of exposure regardless of its chemical form (chloride, carbonate, oxide, sulfide, sulfate, or other forms). Absorption by the dermal route of exposure, however, is relatively insignificant for cadmium, although small amounts are absorbed percutaneously over a long period of time (Wester et al. 1992). Absorption is mainly of concern from inhalation and oral exposures.

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Gastrointestinal tract absorption of cadmium (in any chemical form) is relatively low when compared to the total amount of cadmium absorbed via the inhalation route. In humans, cadmium absorption has been reported to be approximately 1–10% ((Flanagan et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973; Shaikh and Smith 1980; Vanderpool and Reeves 2001). In other species, gastrointestinal tract absorption of cadmium has been determined to be 1–2% in mice and rats (Decker et al. 1958; Ragan 1977), 0.5–3.0% in monkeys (Friberg et al. 1974), 2% in goats (Miller et al. 1969), 5% in pigs and lambs (Cousins et al. 1973; Doyle et al. 1974), and nearly 16% in cattle (Miller et al. 1967). Lehman and Klaassen (1986) investigated the dose-dependence of cadmium absorption and disposition in male Sprague-Dawley rats. Cadmium absorption was estimated to be 0.35 and 1% following oral exposure to 1 or 10,000 µg/kg, respectively. Goon and Klaassen (1989) measured absorption of cadmium in rat intestine *in situ* and reported that the intestinal absorption of cadmium is dosage independent at low dosages of cadmium (<10 µg/kg) and dosage dependent at high dosages (>10 µg/kg). They also evaluated the role of metallothionein and concluded that saturation of intestinal metallothionein is not a major determinant of the observed dosage-dependent absorption of cadmium.

Although the mechanism involved in the intestinal absorption of cadmium has not been fully elucidated, there is evidence that one or more transporter proteins are involved. Several studies have found evidence that divalent metal transporter I protein plays an important role in the gastrointestinal absorption of cadmium (Kim et al. 2007; Park et al. 2002; Ryu et al. 2004). However, studies in knockout mice suggest that other transporter proteins are involved with cadmium absorption (Min et al. 2008; Ryu et al. 2004; Suzuki et al. 2007).

In some cases, cadmium bound to metallothionein (as in food) is not absorbed or distributed from the gastrointestinal tract as readily as ionic cadmium. Mice had lower blood and liver cadmium levels from oral exposure to cadmium-metallothionein, compared to levels from cadmium chloride exposure for comparable doses, but the cadmium-metallothionein resulted in higher kidney cadmium levels. Sharma et al. (1983) reported that human exposure to very high intakes of cadmium during the consumption of oysters resulted in increases in whole blood and urine cadmium levels; however, the increase was not proportional to the level of intake.

A higher fraction of inhaled cadmium than ingested cadmium is absorbed. The total amount of cadmium absorbed by the body via the lungs depends on the particle size. Larger particles are deposited in the nasopharyngeal and tracheobronchial airways via impaction, and are largely cleared by mucociliary processes, leading to absorption by the gastrointestinal tract. Smaller particles reach the smaller airways

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and alveoli, and depending on the particle's solubility, are absorbed and distributed to the rest of the body. Solubility in lung fluids plays a role in absorption from the lung into the body of cadmium salts.

Theoretically, the highly soluble salts, chloride, nitrate, acetate, and sulfate would be expected to give the highest blood levels following inhalation exposure to a given air concentration. The insoluble cadmium salts, the various sulfides, should yield the lowest blood level. The lung, however, is rich in carbon dioxide that is continuously transferred from the blood. Particles of the various cadmium sulfides within the lung can react with this carbon dioxide. Lung tissue may then absorb and transfer solubilized or released cadmium ions to the blood.

No direct data, however, are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure, 5–20% after 15 minutes to 2 hours (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986), due to the absorption of cadmium and the lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in the lung differs somewhat among chemical forms, but the pattern apparently does not correlate well with solubility in water (Glaser et al. 1986; Rusch et al. 1986). Retention of cadmium has been reported to be >40% in rats (Moore et al. 1973), 40% in canines (Friberg et al. 1974), and 10–20% in mice (Potts et al. 1950).

The cadmium levels in cigarettes range from 0.28 to 3.38 µg (Elinder et al. 1985b; Watanabe et al. 1987); the mean in 38 U.S. brands was 1.07 µg (Watanabe et al. 1987). Approximately 10% of the cadmium in cigarettes is inhaled (Elinder et al. 1985b). Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorptions of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985).

Distribution and Metabolism. Absorbed cadmium is distributed throughout the body, with the highest concentrations found in the liver and kidneys. Cadmium is not known to undergo direct metabolic conversions. It has a high affinity for the sulfhydryl groups of albumin and metallothionein (Nordberg et al. 1985). The interaction between cadmium and metallothionein plays a critical role in the

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toxicokinetics and toxicity, as discussed in Section 3.5.2, of cadmium. Metallothionein sequesters a large fraction of tissue cadmium (Shaikh 1982) and studies in metallothionein transgenic and metallothionein-null mice suggest that metallothionein influences tissue retention, but may not affect cadmium distribution to the liver, kidney, pancreas, or spleen (Liu and Klaassen 1996; Liu et al. 1996; Wong and Klaassen 1980a). Metallothionein turns over with half-lives of 2.8 days in the rat liver and 5 days in the kidney (Shaikh and Smith 1976); however, cadmium is retained in both organs bound mainly to metallothionein. It has a retention half-time of 73 days in the liver and a life-time in the kidneys (Shaikh 1982).

Shaikh et al. (1993) report that disposition of cadmium in mouse liver, kidney, and testes is different for different strains, sex, or age. Different dose levels (i.e., subcutaneous doses in the 5–30 $\mu\text{mol/kg}$ body weight range) also altered the disposition. Liver cadmium levels and metallothionein levels did not always correlate with hepatotoxicity. The difference in the tissue accumulation of cadmium may relate to variations in the hormonal or other intrinsic factors that affect cellular uptake of cadmium, subcellular distribution of cadmium, or metallothionein metabolism.

Excretion. Since a small fraction of the cadmium presented to the gastrointestinal tract is absorbed, most of the oral dose is excreted via the feces. After inhalation exposure to cadmium, the initial lung burden of cadmium-laden particles depositing in the nasopharyngeal or central airways will be cleared via the mucociliary mechanisms, possibly undergoing a small amount of absorption by the oral route. The remaining cadmium particles will be absorbed in the lung. Once absorbed cadmium has distributed throughout the body (primarily to the liver and kidney), the amounts of fecal and urinary excretion of cadmium are approximately equal. The amount of cadmium in the urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion increases markedly (Roels et al. 1981b).

Klaassen and Kotsonis (1977) evaluated biliary excretion of an intravenous bolus of cadmium chloride in the rat, rabbit, and dog. Marked species variation in biliary excretion was observed with rabbits at about 1/6th the rate of the rats, and dogs about 1/300th the rate of the rats. In the rat, the bile/plasma concentration ratio of cadmium was highly dose dependent, increasing with higher dose; at 0.1 mg/kg, the bile/plasma ratio was 2.6 and at 3.0 mg/kg, the bile/plasma ratio was 133. The bile/liver concentration ratio of cadmium was equal to or much lower than 1 decreasing to <1% for the low dose regimen.

3.5.2 Mechanisms of Toxicity

Cadmium is toxic to a wide range of organs and tissues; however, the primary target organs of cadmium toxicity are the kidneys; bone and lung (following inhalation exposure) are also sensitive targets of toxicity. Changes in the kidney due to cadmium toxicity have been well established. Chronic exposure to cadmium by the oral or inhalation routes has produced proximal tubule cell damage, proteinuria (mainly low-molecular weight proteins, such as β 2-microglobulin), glycosuria, amino aciduria, polyuria, decreased absorption of phosphate, and enzymuria in humans and in a number of laboratory animal species. The clinical symptoms result from the degeneration and atrophy of the proximal tubules, or (in worse cases) interstitial fibrosis of the kidney (Stowe et al. 1972). Cadmium has been shown to perturb lipid composition and enhance lipid peroxidation (Gill et al. 1989b). Depletion of antioxidant enzymes, specifically glutathione peroxidase and superoxide dismutase, has been proposed as the mechanism of cadmium's cardiotoxic effects (Jamall and Smith 1985a), but subsequent studies showed that cardiotoxic mechanisms other than peroxidation are also present (Jamall et al. 1989). Cadmium has been shown to alter zinc, iron and copper metabolism (Petering et al. 1979) as well as selenium (Jamall and Smith 1985b). Xu et al. (1995) propose that an initiating step in cadmium-induced toxicity to the testes is cadmium interference with zinc-protein complexes that control DNA transcription which subsequently leads to apoptosis. Cadmium sequestration by metallothionein (or a chelator in the case of the Xu et al. [1995] study) prevents cadmium from disrupting zinc-dependent transcriptional controls.

Cardenas et al. (1992a) investigated a cadmium-induced depletion of glomerular membrane polyanions and the resulting increased excretion of high-molecular-weight proteins. Interference with glomerular membrane polyanionic charge may precede the tubular damage as a more sensitive and early response to cadmium (Roels et al. 1993). Acute or chronic doses of cadmium have also been reported to reduce hepatic glycogen stores and to increase blood glucose levels. Intralobular fibrosis, cirrhosis, focal mononuclear infiltrates, and proliferation of the smooth endoplasmic reticulum are among the nonspecific histopathological indicators of cadmium toxicity.

Cadmium complexed with metallothionein from the liver can redistribute to the kidney (Dudley et al. 1985). When metallothionein-bound cadmium is transported to the kidney, it readily diffuses and is filtered at the glomerulus, and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). In the kidneys, exogenous metallothionein is degraded in lysosomes and released cadmium is sequestered by the endogenous metallothionein as well as other proteins (Cherian

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and Shaikh 1975; Squibb et al. 1984; Vestergaard and Shaikh 1994). This non-metallothionein-bound cadmium can then induce new metallothionein synthesis in the proximal tubule (Squibb et al. 1984).

Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). The rate of metallothionein synthesis in the kidney is lower than in the liver (Sendelbach and Klaassen 1988), and is thought to be insufficient, at some point, to bind the intrarenal cadmium (Kotsonis and Klaassen 1978). Renal damage is believed to occur when the localization of cadmium, or an excessive concentration of cadmium, is unbound to metallothionein. Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage as described above (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present.

Dorian et al. (1992a) evaluated the intra-renal distribution of 109 cadmium-metallothionein injected (intravenously) into male Swiss mice at a nonnephrotoxic dose (0.1 mg Cd/kg) and concluded that cadmium-metallothionein-induced nephrotoxicity might be due, at least in part, to its preferential uptake of cadmium-metallothionein into the S1 and S2 segments of the proximal tubules, the site of cadmium-induced nephrotoxicity. In a companion study, Dorian et al. (1992b) reported that this preferential renal uptake was also observed after administration of various doses of [35 S]cadmium-metallothionein. In contrast to the earlier observed persistency of 109 cadmium in the kidney after 109 cadmium-metallothionein administration, however, 35 S disappeared rapidly (with a half-life of approximately 2 hours); 24 hours after injection of [35 S]cadmium-metallothionein, there was very little 35 S left in the kidneys. These observations indicate that the protein portion of cadmium-metallothionein is rapidly degraded after renal uptake of cadmium metallothionein and that the released cadmium is retained in the kidney.

The toxic effects and distribution of cadmium were compared after intravenous injection of 109 cadmium-metallothionein at 0.05–1 mg Cd/kg body weight and 109 cadmium chloride at 0.1–3 mg/kg in male Swiss mice (Dorian et al. 1995). Cadmium-metallothionein increased urinary excretion of glucose, and protein indicated renal injury, with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by cadmium chloride administration, even at dosages as high as 3 mg Cd/kg. Cadmium-metallothionein distributed almost exclusively to the kidney, whereas cadmium chloride preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after cadmium chloride administration (i.e., the renal cadmium concentration after administration of a high but nonnephrotoxic

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dose of cadmium chloride was equal to or higher than that obtained after injection of nephrotoxic doses of cadmium-metallothionein). Light microscopic autoradiography studies indicated that cadmium from cadmium-metallothionein preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from cadmium chloride distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after cadmium chloride than after cadmium-metallothionein administration. A higher cadmium concentration in both apical and basal parts of the proximal cells was found after cadmium chloride than after cadmium-metallothionein administration. The authors suggest that cadmium-metallothionein is nephrotoxic, and cadmium chloride is not nephrotoxic because of a higher concentration of cadmium in the target cells after cadmium-metallothionein. Dorian and Klaassen (1995) evaluated the effects of zinc-metallothionein on ¹⁰⁹cadmium-metallothionein renal uptake and nephrotoxicity and concluded that zinc-metallothionein is not only nontoxic to the kidney at a dose as high as 5 µmole metallothionein/kg, but it can also protect against the nephrotoxic effect of cadmium-metallothionein without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a cadmium-metallothionein complex, Liu et al. (1998) exposed metallothionein-null mice to a wide range of cadmium chloride doses, 6 times/week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 µg Cd/g kidney in control mice (i.e., metallothionein normal) with a 150-fold increase in renal metallothionein levels (800 µg metallothionein/g kidney). Renal cadmium was much lower in metallothionein-null mice (10 µg Cd/g), and metallothionein levels were not detectable. The maximum tolerated dose of cadmium (as indicated by routine urinalysis and histopathology measures) was approximately 8 times higher in control mice than in metallothionein-null mice. Lesions were more severe in metallothionein-null mice than in controls.

The critical concentration of cadmium in the renal cortex that is likely to produce renal dysfunction also remains a topic of intense investigation. Whether the critical concentration of urinary cadmium is closer to 5 or 10 µg Cd/g creatinine, corresponding to about 100 and 200 µg cadmium/g kidney, respectively, is the current focus of the debate. In one analysis, the critical concentration producing dysfunction in 10% of a susceptible population has been estimated to be approximately 200 µg cadmium/g kidney; 50% of the susceptible population would experience dysfunction with a kidney concentration of 300 µg/g (Ellis et al. 1984, 1985; Roels et al. 1983).

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Studies in humans and animals have demonstrated that the bone is a sensitive target of cadmium toxicity. It is likely that cadmium acts by direct and indirect mechanisms, which can lead to decreased bone mineral density and increased fractures (Brzóska and Moniuszko-Jakoniuk 2005c, 2005d). Studies in young animals suggest that cadmium inhibits osteoblastic activity, resulting in a decrease in the synthesis of bone organic matrix and mineralization (Brzóska and Moniuszko-Jakoniuk 2005d). The decreased osteoblastic activity may also influence osteoclastic activity leading to increased bone resorption. During intense bone growth, effects on osteoblasts result in decreased bone formation; after skeletal maturity, cadmium exposure results in increased bone resorption. Cadmium-induced renal damage can also result in secondary effects on bone (Brzóska and Moniuszko-Jakoniuk 2005c). Cadmium-induced renal damage interferes with the hydroxylation of 25-hydroxy-vitamin D to form 1,25-dihydroxy-vitamin D. Decreased serum concentration of 1,25-dihydroxy-vitamin D, along with impaired kidney resorptive function, result in calcium and phosphate deficiency (via decreased gastrointestinal absorption and increased calcium and phosphate urinary loss). To maintain calcium and phosphate homeostasis, parathyroid hormone is released, which enhances bone resorption.

3.5.3 Animal-to-Human Extrapolations

The effects of cadmium exposure have been studied in humans and in many laboratory animal species. The target organs are similar among species, with the kidneys, bone, and lungs (inhalation only) being the primary organs for cadmium induced toxicity. Absorption, distribution, and excretion of cadmium after oral and inhalation exposures are roughly similar among species; however, there are some notable differences and caveats. Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. Differences in the breathing patterns between rats (obligatory nose breathers) and humans (mouth and nose breathers) may also result in radically different lung burden patterns (and hence, different absorption profiles) of cadmium particles in the lungs. Many of the common laboratory animals (in particular the mouse and rat) provide useful information on the toxic effects of cadmium; due to their relatively short lifespan, however, they may not be as useful from a risk assessment point of view in determining the human lifetime effects from inhaling cadmium in air, or ingesting it in food and water. Rates of synthesis and inducibility of metallothionein also differ among species, sex, and target organ.

Even within species there can be significant differences in metallothionein synthesis, and these differences correlate to the degree of cadmium toxicity observed (e.g., the mouse) (Shaikh et al. 1993). The Shaikh et al. (1993) study employed acute exposures. Strain differences in carcinogenic effects have

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also been reported for chronic exposures of subcutaneously administered cadmium chloride in male DBA and NFS mice. DBA mice developed lymphomas, while NFS mice developed hepatocellular adenomas and carcinomas, and sarcomas at the injection site. Both strains developed nonneoplastic testicular lesions (fibrosis and mineralization) (Waalkes and Rhem 1992).

Metal-metal interactions are also an important factor in cadmium kinetics and toxicity, and organ specific metal concentrations and metabolism can differ among species. It is thought that further development of PBPK/PD models will assist in addressing these differences and in extrapolating the animal data to support risk assessments in humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997a). Stated differently, such compounds may cause toxicities that

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are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to cadmium.

No *in vitro* studies were located regarding endocrine disruption of cadmium.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are

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proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Occupational and environmental exposure studies in adults provide strong evidence that the lung (inhalation exposure only) and kidneys are sensitive targets of toxicity; it is likely that these effects would also be seen in children. Because cadmium is a cumulative toxin and has a very long half-time in the body, exposures to children in even low amounts may have long-term adverse consequences. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40–50 µg/g wet weight) between the ages of 50 and 60 years, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). There are limited data on the renal toxicity of cadmium in children. One study found significant associations between urinary and blood cadmium levels with urinary levels of NAG and retinol binding protein (de Burbure et al. 2006); however, the investigators cautioned that the early response observed in this group of children exposed to elevated levels of cadmium (and other metals) may reflect an early renal response that may be adaptive and/or reversible. Another study (Trzcinka-Ochocka et al. 2004) found higher urinary concentrations of β2-microglobulin and retinol binding protein in a population exposed to high

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levels of cadmium starting in childhood as compared to a group only exposed as adults even though urinary cadmium levels were lower (statistical comparisons of urinary cadmium levels were not made between the groups). These data suggest that adults exposed to cadmium as children may be more susceptible to the renal toxicity of cadmium than persons only exposed as adults. This is supported by the findings of Jacquillet et al. (2007) of renal damage in mature rats exposed to cadmium via gestation and lactation.

There are epidemiological data suggesting that the bone is also a sensitive target of cadmium toxicity (Åkesson et al. 2005; Alfvén et al. 2000, 2002a, 2004; Aoshima et al. 2003; Jin et al. 2004b; Nordberg et al. 2002; Staessen et al. 1999; Wang et al. 2003; Zhu et al. 2004). Epidemiology studies suggest that the elderly may be more susceptible than younger adults; however, no studies examined childhood exposure. Animal studies suggest that young animals are more susceptible than adult or elderly animals (Ogoshi et al. 1989).

A potential for cadmium to have adverse neurological effects is an important consideration. However, only a few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), and acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985). The usefulness of the data from these studies is limited, however, because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and inadequate quantification of cadmium exposure (i.e., the studies used hair cadmium as an index of exposure, which has some limitations because of potential confounding from exogenous sources). Several animal studies have reported alterations in performance on neurobehavioral tests in rats exposed to cadmium via gestation and lactation (Ali et al. 1986; Baranski et al. 1983; Desi et al. 1998; Nagymajtenyi et al. 1997). Several studies have examined the possible association between cadmium exposure and newborn birth weight, and most reliable studies have not found a significant association (Galicía-García et al. 1997; Mokhtar et al. 2002; Nishijo et al. 2002, 2004b; Zhang et al. 2004). Animal studies have found significant decreases in body weight or skeletal anomalies or malformations in the offspring of rats exposed to high doses of cadmium (Ali et al. 1986; Baranski 1985, 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Machemer and Lorke 1981; Petering et al. 1979; Pond and Walker 1975; Schroeder and Mitchener 1971; Sorell and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988).

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Oral cadmium exposure has also been reported to suppress the T-lymphocyte and macrophage-dependent humoral immune response of 6-week-old mice against sheep red blood cells (Blakley 1985), but not of 12-month-old mice (Blakley 1988). The investigators cautioned that “natural” age-related immune system dysfunction may have masked any cadmium suppressive effect.

Children are most likely to be exposed to cadmium in food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. In adults, only about 1/20 of the total ingested cadmium (in food or water) is absorbed (McLellan et al. 1978, Rahola et al. 1973; Shaikh and Smith 1980). The retention of cadmium in the gut slowly decreases over a period of 1–3 weeks after ingestion in adults (Rahola et al. 1973). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs.

Tissue distribution and retention of cadmium differed between 4- and 70-day-old rats. Cadmium was 3–6 times more concentrated in the newborn spleen, bone, brain, testes, and muscle than in the adult rat 2 hours after an intravenous administration of 1 mg Cd/kg body weight. Liver concentration of metallothionein was 20 times greater in the newborn than in the adult; kidney metallothionein concentrations were comparable, but liver cadmium was only 30% higher and kidney cadmium was 50% higher in the newborn. Nineteen days post-cadmium exposure, the retention of cadmium in the liver, kidney, and lung was similar in both the newborn and the adult rat (Wong and Klaassen 1980a). Goering and Klaassen (1984b) report that high levels of metallothionein in 10-day-old rats play an important role in their resistance to liver damage, presumably by binding and retaining cadmium. However, the tissue distribution data led Wong and Klaassen (1980a) to propose that metallothionein does not play a major role in the tissue distribution and retention of cadmium in the young.

Cadmium can be transferred to offspring in breast milk. Cadmium levels in human milk are 5–10% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987). A significant association between urinary cadmium levels and cadmium levels in breast milk was found in women environmentally exposed to cadmium (Nishijo et al. 2002). In female outbred albino rats exposed to cadmium in drinking water (as cadmium chloride) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, 3 weeks of gestation, or 3 weeks into lactation), kidney concentrations exceeded liver concentrations, while in their pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium

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concentrations considerably increased only during the second half of the lactation period (Ld 11–21). The cadmium tissue concentrations in dams were several orders higher than in offspring. Another study found a positive correlation between cadmium levels in breast milk and cadmium levels in the pups' kidneys in rats receiving an intravenous injection of cadmium on lactation days 3–16 (Petersson Grawé and Oskarsson 2000).

Although studies on elimination of cadmium from the tissues of children are not available, the results of studies in animals provide some insight. Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. Of the cadmium that is absorbed into the body, most is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellström and Nordberg 1978). Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years (Kjellström and Nordberg 1985). Half-times in the slowest phase were 20–50% of the maximum life span of the animal (Kjellström and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellström and Nordberg (1985) developed a range of half-times from their kinetic model of between 6 and 38 years for the human kidney and between 4 and 19 years for the human liver. These high values indicate the persistence of cadmium in the body and the importance of minimizing exposures in children to prevent long-term accumulation and toxicity.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in another study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental cadmium concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sorell and Graziano 1990). Thus, timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies.

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Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule and is inducible in most tissues by exposure to cadmium, zinc, and other metals (Waalkes and Goering 1990). Metallothionein binding decreases the toxicity of cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). Goyer and Cherian (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Chan and Cherian (1993) report that pregnancy in Sprague-Dawley rats previously administered cadmium chloride (1.0 mg Cd/kg body weight subcutaneously, daily for 8 days) leads to a mobilization of cadmium from the liver (40% decrease compared to nonpregnant cadmium treated controls) and an increase in the kidneys (60% increase). A similar pattern is seen for metallothionein. Plasma cadmium and metallothionein also increased in the pregnant group. Placental cadmium increased in the cadmium-treated rats compared to the untreated controls. In this rat model, then, pregnancy resulted in a transfer of hepatic cadmium and metallothionein via the blood to the kidney and placenta.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at <http://www.cdc.gov/exposurereport/>. The biomonitoring data for cadmium from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure

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are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cadmium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cadmium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Cadmium

Cadmium levels in blood, urine, feces, liver, kidney, hair, and other tissues have been used as biological indicators of exposure to cadmium. A discussion of the utility and limitations of each for human biomonitoring is provided below.

Blood cadmium levels are principally indicative of recent exposure(s) to cadmium rather than whole-body burdens (Ghezzi et al. 1985; Järup et al. 1988; Lauwerys et al. 1994; Roels et al. 1989). The 50th

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percentile of blood cadmium concentrations in adults living in the United States was 0.330 µg/L (CDC 2011). Environmental exposure can elevate blood cadmium concentration to above 10 µg/L (Kido et al. 1990a, 1990b; Shiwen et al. 1990). Workers occupationally exposed to cadmium by inhalation may have blood cadmium levels ranging up to 50 µg/L (Roels et al. 1981b).

Urine cadmium levels primarily reflect total body burden of cadmium, although urine levels do respond somewhat to recent exposure (Bernard and Lauwerys 1986). Use of a biokinetic model, such as the Nordberg-Kjellström model, allows estimation of cadmium dietary consumption or airborne cadmium levels from urinary cadmium levels; these models are described in greater detail in Section 3.4.5.3. When the critical level for renal damage has been reached, urinary cadmium levels rise sharply because of the release of intrarenal cadmium along with decreased renal reabsorption of cadmium (Lauwerys et al. 1994; Roels et al. 1981b). In the U.S. general population, the geometric mean urinary cadmium level in adults is 0.232 µg/L (or 0.247 µg/g creatinine) (CDC 2011). In populations with substantial environmental or occupational exposure, values can range up to 50 µg/g creatinine, (Falck et al. 1983; Roels et al. 1981b; Tohyama et al. 1988). In environmentally exposed individuals, Buchet et al. (1990) report that abnormal values of various biomarkers are found in 5% of the population with urinary excretion of cadmium above the 2–4 µg Cd/24 hour level (approximately 1–3 µg/g creatinine). Significant correlations between total cadmium exposure and urinary cadmium levels have been found in environmentally exposed populations (Kido et al. 2004; Kobayashi et al. 2005; Shimbo et al. 2000). Among environmentally exposed subjects, there was good agreement between urinary cadmium levels measured at different times, suggesting that a single determination would be an accrument measure (Ikeda et al. 2005a).

Fecal cadmium may be used as a direct indicator of daily dietary intake of cadmium because dietary cadmium is poorly absorbed in the gastrointestinal tract (Kjellström et al. 1978). In workers exposed by inhalation, fecal cadmium has been used to estimate the amount of inhaled cadmium transported to the gastrointestinal tract and the amount of dust ingested incidentally at work (Adamsson et al. 1979). Fecal cadmium primarily reflects recently ingested cadmium and, therefore, is not a good indicator of past cadmium exposure (Shaikh and Smith 1984).

Liver and kidney tissues preferentially accumulate cadmium, and concentrations of cadmium in liver and kidney may be measured using non-invasive techniques such as *in vivo* neutron activation analysis or in the kidney by X-ray fluorescence analysis (Christoffersson et al. 1987; Scott and Chettle 1986); however, the limit of detection is near background levels (Nordberg 2010). Levels in both tissues increase with age and level of cadmium exposure, but kidney cadmium concentration tends to peak around age 50–60,

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while liver cadmium concentration continues to rise. Typical values for a 60-year-old North American with average environmental cadmium exposure are 25–40 µg/g wet weight in kidney cortex and 1–3 µg/g wet weight in liver (Elinder 1985b). In workers exposed to cadmium by inhalation, values up to 300 µg/g wet weight in kidney and 100 µg/g wet weight in liver can be found (Christoffersson et al. 1987; Roels et al. 1981b). Because kidney cadmium content begins to decline after the onset of cadmium-induced renal dysfunction, liver cadmium may be a better indicator of cadmium exposure than kidney cadmium, and it has been suggested that kidney dysfunction is likely to appear at liver cadmium concentrations between 30 and 60 µg/g wet weight (Roels et al. 1981b). *In vivo* liver and kidney cadmium measurements involving neutron activation analysis or X-ray fluorescence require complex and costly equipment and may pose a radiation hazard (Shaikh and Smith 1984), and those involving biopsy specimens (Lindqvist et al. 1989) require a painful and invasive procedure. Therefore, these methods for *in vivo* analysis are better suited for monitoring of occupationally exposed workers than environmentally exposed populations (Scott and Chettle 1986). Among cadmium workers, significant correlations of kidney cadmium levels with urinary and blood cadmium levels and liver cadmium with urinary cadmium levels were found (Börjesson et al. 1997, 2001). Similar correlations (urinary cadmium with renal cadmium) in an autopsy study of subjects without occupational exposure to cadmium; a urinary cadmium level of 1.7 µg/g creatinine was equivalent to a renal cadmium level of 50 µg/g (Orlowski et al. 1998).

Hair levels of cadmium have been used as a measure of cadmium exposure, although the possibility of exogenous contamination has led to substantial controversy concerning the reliability of hair levels as a measure of absorbed dose (Frery et al. 1993; Huel et al. 1984; Lauwerys et al. 1994; Shaikh and Smith 1984; Wilhelm et al. 1990). Recent evidence has shown a correlation between cadmium levels in the hair of newborn infants and their mothers (Huel et al. 1984) and between cadmium levels in scalp and pubic hair (Wilhelm et al. 1990), indicating that among environmentally exposed populations, external contamination may not be significant for hair samples taken close to the scalp. Under occupational conditions, external contamination may be a more substantial problem (Shaikh and Smith 1984).

On the other hand, Frery et al. (1993) evaluated hair levels in a male population with a high expected exposure to tobacco smoke and in a population of pregnant woman and their newborns; they concluded that cadmium hair analysis was a reliable indicator for the subjects with the highest exposure, but was not sensitive enough to resolve differences for low level exposures. Newborn cadmium hair levels were a more sensitive indicator than mother's hair, but the research was not able to determine if this was attributable to physiological changes or the lower reliability of the mother's head hair. Exogenous contamination is not considered a problem for newborn hair. The authors state that the variability

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introduced by exogenous contamination can be minimized by using the first 8 cm of hair from the scalp and by using careful washing techniques. There was also no significant difference between hair levels for passive or nonsmokers indicating that either the above mentioned precautions worked or that the passive smoke source of exposure was not significant.

Cadmium measurements have been made on a variety of other biological materials, including milk (Schulte-Lobbert and Bohn 1977; Sikorski et al. 1989), placenta (Kuhnert et al. 1982; Roels et al. 1978; Saaranen et al. 1989), nails (Takagi et al. 1988), teeth (Sharon 1988), and cataractous lenses (Racz and Erdohelyi 1988). Although in some cases it could be established that levels in these tissues were higher among smokers than nonsmokers, the significance of cadmium levels as a marker of recent or total cadmium exposure has not been established for any of these tissues.

Studies in cadmium workers suggest that metallothionein levels may also be a biomarker of cadmium exposure. Elevated levels of metallothionein gene expression were observed in peripheral blood lymphocytes in highly exposed workers. The level of metallothionein gene expression was significantly correlated with blood and urinary cadmium levels (Lu et al. 2001). Urinary metallothionein correlates with cadmium concentrations in liver, kidney, and urine (Shaikh and Smith 1984; Tohyama et al. 1981). Relatively strong correlations have been found between urinary metallothionein and urinary cadmium levels in exposed humans (Kawada et al. 1990), and a dose-related increase in urinary metallothionein was found in rats exposed to cadmium in drinking water for up to 2 years (Shaikh et al. 1989). Hochi et al. (1995) also found a significant relationship between cadmium intake and urinary metallothionein levels among residents consuming cadmium-contaminated rice.

3.8.2 Biomarkers Used to Characterize Effects Caused by Cadmium

Acute inhalation exposure to high levels of cadmium causes respiratory damage and may lead to death. No information was located on biomarkers of respiratory effects in humans, but based on animal experiments, activity of alkaline phosphatase in the surfactant fraction of BALF has been suggested as a sensitive marker of pulmonary damage following acute cadmium inhalation (Boudreau et al. 1989). Such a biomarker of effect is not specific to cadmium exposure and would be most relevant to occupational exposures.

Renal dysfunction, usually first manifested as impaired tubular reabsorption of filtered solutes, is generally considered the primary toxic effect of chronic cadmium exposure (see Section 3.2). Impaired

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kidney function has been measured by increased levels of solutes (proteins, amino acids, uric acid, calcium, copper, phosphorous, etc.) in urine and/or serum. Excess urinary excretion of low-molecular-weight proteins and solutes is associated with decreased tubular reabsorption. Increased excretion of high-molecular-weight proteins or decreased serum clearance of creatinine reflect glomerular dysfunction, which is generally associated with progressive renal damage (Roels et al. 1989). A brief discussion of the utility and limitations of several measures of tubular damage as biomarkers of effects of cadmium exposure is provided below. These biomarkers are normally found in the urine and elevated levels are not specific for cadmium.

Urinary β 2-microglobulin, a low molecular weight protein, has been widely used as an indicator of tubular renal dysfunction (Arisawa et al. 1997; Piscator 1984; Roels et al. 1981a; Smith et al. 1980). However, tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so β 2-microglobulin is not a specific marker of cadmium-induced effects (Shaikh and Smith 1984). Practical considerations in using urinary β 2-microglobulin as a marker of tubular renal dysfunction include the need to control the pH of samples to prevent the rapid degradation that occurs at pH values below 5.5 (Shaikh and Smith 1984), and the fact that urinary β 2-microglobulin excretion normally rises with age (Roels et al. 1989).

Urinary retinol-binding protein is also considered to be a sensitive indicator of decreased tubular reabsorption, but it also is not specific for cadmium-induced damage in the kidney (Shaikh and Smith 1984; Topping et al. 1986). Retinol-binding protein is more stable in urine than β 2-microglobulin (Bernard and Lauwerys 1981) and appears to be of approximately equal sensitivity and specificity for detecting tubular proteinuria in cadmium-exposed populations (Topping et al. 1986). Levels of both proteins fluctuate over time, so regular, repeated sampling may be necessary to establish abnormal levels (Ormos et al. 1985).

Human complex-forming glycoprotein (pHC, also referred to as α ₁-microglobulin) is another sensitive marker of tubular renal dysfunction (Moriguchi et al. 2004, 2005a; Pless-Mulloli et al. 1998; Tohyama et al. 1986). As with retinol binding protein, pHC is more stable in urine than β 2-microglobulin at room temperature and low urinary pH levels.

Urinary N-acetyl- β -D-glucosaminidase (NAG), a lysosomal enzyme present in high concentrations in the proximal tubule, has been shown to correlate with urinary cadmium levels in occupationally and environmentally exposed subjects (Jin et al. 1999; Kalahasthi et al. 2007) and has a better correlation with

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urinary cadmium levels than does β 2-microglobulin at low cadmium exposure levels (urinary cadmium $<10 \mu\text{g/g}$ creatinine) (Chia et al. 1989; Kawada et al. 1990; Mueller et al. 1989). However, increased urinary NAG activity can result from effects other than nephrotoxicity (Bernard and Lauwerys 1989). Jin et al. (1999) suggest that measurement of the B isozyme (NAG-B), which is released into the urine following tubular cell breakdown, may be a sensitive measure of renal damage.

Other enzymes, proteins, and amino acids in urine have been suggested as biological markers of incipient renal or liver damage resulting from cadmium exposure. Markers found to be sensitive indicators in exposed humans include trehalase (Iwata et al. 1988), alanine aminopeptidase (Mueller et al. 1989), and calcium (Buchet et al. 1990). Changes in urinary alkaline phosphatase, γ -glutamyl transferase, urate, and phosphate tend to be significant only after other markers of renal damage are clearly elevated (Mason et al. 1988). Several other enzymatic markers of cadmium-induced renal damage have been suggested based on animal studies (Bomhard et al. 1984; Gatta et al. 1989; Girolami et al. 1989). Aminoaciduria has been found to be more sensitive than proteinuria for renal damage in animal studies (Nomiyama et al. 1975), but less sensitive in humans (Axelsson and Piscator 1966). Recent work by Prozialeck et al. (2007) suggest that kidney injury molecule 1 may be a sensitive marker for renal dysfunction. At present, not enough information is available to determine which, if any, of these parameters provide sensitive and specific indicators of cadmium-induced renal damage.

At the present time, there is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted except at high exposure levels. Measurement of a variety of markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause.

There is also considerable controversy as to whether the critical concentration of urinary cadmium is closer to 5 or 10 $\mu\text{g Cd/g}$ creatinine, corresponding to about 100 and 200 ppm in the kidney, respectively. Roels et al. (1993) correlated a number of markers with cadmium in blood and urine in a study population of workers occupationally exposed to cadmium from cadmium smelting operations. Three main groupings of thresholds were identified corresponding with different markers of effects: one around 2 $\mu\text{g Cd/g}$ creatinine mainly associated with biochemical alterations (increased urinary 6-keto-prostaglandin F_{1x} and urinary sialic acid), a second around 4 $\mu\text{g Cd/g}$ creatinine associated with increased excretion of high molecular weight proteins (possibly due to disruption of the glomerular membrane polyanionic

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charge) and tubular antigens or enzymes (BBA, NAG), and a third around 10 µg Cd/g creatinine associated with increased excretion of low molecular weight proteins and other indicators. The 10 µg Cd/g creatinine level had previously been proposed as the biological threshold for cadmium-induced nephropathy. Whether the earlier changes are indicative of irreversible adverse renal effects remains an area of continued investigation.

To further evaluate the reversibility of proteinuria, Roels et al. (1997) studied the progression of cadmium-induced renal tubular dysfunction in cadmium workers according to the severity of the microproteinuria at the time the exposure was substantially decreased. A total of 32 cadmium male workers were divided into two groups on the basis of historical records of urinary cadmium concentration (CdU) covering the period until 1984. The workers with CdU values of >10 µg Cd/g creatinine were subdivided further on the basis of the urinary concentration of β₂-microglobulin (β₂-MG-U) measured during the first observation period (1980–1984). In each group, the tubular microproteinuria as reflected by β₂-MG-U and the concentration of retinol-binding protein in urine as well as the internal cadmium dose as reflected by the concentration of cadmium in blood and urine were compared between the first and second (1990–1992) observation periods. Increased microproteinuria was often diagnosed in cases with CdU values of >10 µg Cd/g creatinine. The progression of tubular renal function was found to depend on the extent of the body burden of cadmium (as reflected by CdU) and the severity of the initial microproteinuria at the time high cadmium exposure was reduced or ceased. When cadmium exposure was reduced and β₂-MG-U did not exceed the upper reference limit of 300 µg/g creatinine, the risk of developing tubular dysfunction at a later stage was likely to be low, even in cases with historical CdU values occasionally >10 but always <20 µg Cd/g creatinine. When the microproteinuria was mild (β₂-MG-U >300 and ≤1,500 µg/g creatinine) at the time exposure was reduced, and the historical CdU values had never exceeded 20 µg Cd/g creatinine, there was indication of a reversible tubulotoxic effect of cadmium. When severe microproteinuria (β₂-MG-U >1,500 µg/g creatinine) was diagnosed in combination with historical CdU values exceeding 20 µg Cd/g creatinine, Cd-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure.

For more information on biomarkers for renal and hepatic effects of chemicals see Agency for Toxic Substances and Disease Registry *Subcommittee Report on Biological Indicators of Organ Damage* (Agency for Toxic Substances and Disease Registry 1990a). For information on biomarkers for neurological effects see OTA (1990).

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3.9 INTERACTIONS WITH OTHER CHEMICALS

Cadmium toxicity can be influenced by a wide variety of other chemicals. In humans, dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects following cadmium exposure (Kjellström 1986c). Iron deficiency has been shown to increase gastrointestinal absorption of cadmium in humans (Flanagan et al. 1978), while oral zinc supplementation has been demonstrated to decrease the oral absorption of cadmium. No other information was located concerning interaction of cadmium with other chemicals in humans.

In animals, a few interactions following inhalation exposure have been evaluated. In rats exposed to cadmium chloride by inhalation, simultaneous exposure to zinc oxide prevents fatalities (Oldiges and Glaser 1986) and lung cancer (Oldiges et al. 1989). Exposure to an atmosphere containing 80% oxygen aggravated pulmonary damage from cadmium chloride inhalation in mice (Martin and Witschi 1985).

The toxicity of oral exposure to cadmium in animals has been shown to be influenced by several factors. In Japanese quail, cadmium toxicity was intensified by single or combined deficiencies of zinc, copper, iron, calcium, and protein (Fox et al. 1979). A calcium-deficient diet in animals has been shown to aggravate cadmium immunotoxicity (Chopra et al. 1984) and fetotoxicity (Pond and Walker 1975). Simultaneous exposure to lindane increased the developmental toxicity of cadmium in rats (Saxena et al. 1986). Female rats have an increased susceptibility to cadmium-induced bone loss due to multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b) or ovariectomy (Bhattacharyya et al. 1988c), possibly related to associated effects on trace element status. Hopf et al. (1990) report that exposure to ethanol and cadmium in a liquid diet produced liver damage in rats at doses that were not separately hepatotoxic. In contrast, Kershaw et al. (1990) reported that ethanol pretreatment in male Sprague-Dawley rats substantially reduced the lethal and hepatotoxic properties of cadmium, possibly due to a reduced interaction between cadmium and target sites in liver organelles and cytosolic high-molecular-weight (HMW) proteins. Ethanol pretreatment in this study decreased (approximately 60%) the content of cadmium in nuclei, mitochondria, and endoplasmic reticulum, and nearly eliminated the association of cadmium with cytosolic HMW proteins. Reduction in the concentration of cadmium in potential target sites of intoxication was caused by a metallothionein-promoted sequestration of cadmium to the cytosol.

When cadmium is co-administered with ethanol in rats, there is a pronounced increase in cadmium accumulation in various regions of the brain (e.g., the corpus striatum and cerebral cortex). The cadmium is not bound to metallothionein, and there is a marked increase in lipid peroxidation and inhibition of

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membrane bound enzymes (Pal et al. 1993a, 1993b). Rats pretreated with acetaminophen are more sensitive to the renal toxicity of cadmium in water (Bernard et al. 1988a). Co-administration of lead and cadmium in the diet of rats had additive effects in reducing body weights, but neurologic toxicity was antagonized (Nation et al. 1990).

Numerous interactions have been demonstrated in animals using parenteral exposure, generally indicating that induction of metallothionein by pretreatment with zinc, selenium, or other metals, reduces toxicity of parenteral cadmium exposure (Gunn et al. 1968a, 1968b; Naruse and Hayashi 1989; Yamane et al. 1990). Zinc, calcium, or magnesium can prevent injection site, testicular, and prostatic cancers induced by subcutaneous or intramuscular injection of cadmium, but these interactions have been shown to be a complex phenomenon, dependent on dose, route, and target organ (Poirier et al. 1983; Waalkes et al. 1989). Mn(II) pretreatment reduces Cd(II)-induced lethality (Goering and Klaassen 1985). Cadmium has been noted to have an inhibitory effect on manganese uptake (Gruden and Matausic 1989). In addition, manganese appears to be capable of increasing the synthesis of the metal-binding protein metallothionein (Waalkes and Klaassen 1985). Data from a study by Goering and Klaassen (1985) suggest that manganese pretreatment increases the amount of Cd^{+2} bound to metallothionein, thereby decreasing hepatotoxicity due to unbound Cd^{+2} . The significance of these observations to humans exposed to cadmium and manganese by the oral or inhalation routes is not clear.

Induction of hepatic metallothionein by cold stress reduced the acute toxicity of cadmium given by gavage to mice (Baer and Benson 1987). In addition to effects on metallothionein induction, substances may interact with cadmium by altering the competition among metal ions for enzyme or regulatory protein binding sites. For example, simultaneous administration of garlic (which is high in reduced sulfhydryl groups) decreases oral cadmium renal toxicity in rats (Cha 1987).

Coexposure to selenium reduced the clastogenic effect of cadmium on mouse bone marrow (Mukherjee et al. 1988b). Selenium deficiency enhances cadmium-induced cardiotoxicity possibly mediated via lipid peroxidation indicated by a significant reduction in the activities of the selenoenzyme, glutathione peroxidase. Selenium supplements in the diet prevented cadmium's cardiotoxic effect (Jamall and Smith 1985a). Selenium has also been shown to prevent testicular damage in rats (Kar et al. 1960; Omaye and Tappel 1975). In testes, selenium as selenite given before or during cadmium administration was shown to divert the binding of cadmium from low molecular proteins to higher molecular weight proteins (Chen et al. 1975; Whanger 1992). In contrast, Jamall and Smith (1985c) report a shift in cadmium binding from metallothionein to lower weight proteins in kidney and liver from a diet supplemented with

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selenium compared to a selenium deficient diet. The selenium-cadmium interaction thus appears to be dependent on the duration and sequence of coexposure and possibly the organ-specific levels of selenoenzymes or other essential metals.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cadmium than will most persons exposed to the same level of cadmium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in increased absorption, reduced detoxification or excretion of cadmium, or compromised function of organs affected by cadmium. Populations who are at greater risk due to their unusually high exposure to cadmium are discussed in Section 6.7, Populations with Potentially High Exposures.

Differences in individual sensitivity to cadmium have not been systematically studied, but based on what is known about cadmium toxicity, some inferences can be made. Populations with depleted stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies could be expected to have increased cadmium absorption from the gastrointestinal tract. Urinary cadmium levels have been shown to be correlated with iron status among pregnant women (Åkesson et al. 2002). However, a general population study of women living in Japan (Tsukahara et al. 2003) did not find significantly elevated levels of urinary cadmium, β 2-microglobulin, or pHc among women with anemia or iron deficiency, as compared to healthy women. Populations with kidney damage from causes unrelated to cadmium exposure, including diabetes, some drugs and chemicals, and the natural age-related decline in kidney function, could be expected to exhibit nephrotoxicity at lower cadmium exposures than those of normal healthy adults (Buchet et al. 1990). There is also some evidence to suggest that diabetics may be more susceptible to the toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990; Haswell-Elkins et al. 2008). Elevated levels of metallothionein-antibody have been significantly associated with excretion of biomarkers of tubular dysfunction among cadmium workers (Chen et al. 2006a), but not with urinary or blood cadmium levels. In a study of diabetics, metallothionein-antibodies were significantly associated with urinary levels of β 2-microglobulin levels, which were indicative of cadmium toxicity but not with urinary albumin levels, which would be indicative of glomerular damage (Chen et al. 2006c). However, a significant association between elevated albumin creatinine ratio and urinary cadmium levels was found in another study of diabetics (Haswell-Elkins et al. 2008) and the frequency of albuminuria

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was 64% among diabetics with high urinary cadmium levels of 1–2 µg/g creatinine and 80% among those with urinary cadmium levels of >2 µg/g creatinine.

A discussion of the susceptibility of children is found in Section 3.7, Children's Susceptibility.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cadmium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cadmium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cadmium:

Caravati EM, McGuigan MA, MacGregor Whyte I, et al. Cadmium fume pneumonitis. In: Medical toxicology, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1411-1414.

Leikin JB, Paloucek FP. 2002. Cadmium. In: Poisoning and toxicology handbook. Hudson, OH: Lexi-Comp, Inc., 309-310.

Viccellio P. 1998. Cadmium, mercury, and arsenic. In: Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 379-380.

3.11.1 Reducing Peak Absorption Following Exposure

Inhalation exposure to high concentrations of cadmium can be particularly dangerous because initial symptoms are often as mild as those associated with low-level exposure, and exposed individuals who are unaware either of the presence of cadmium or of the dangers of inhaling cadmium may allow exposure to continue until a harmful or even fatal dose is received (Beton et al. 1966; Lucas et al. 1980). Severe respiratory symptoms that may develop within a few hours of high-dose inhalation exposure include tracheobronchitis, pneumonitis, and pulmonary edema, accompanied by additional nonspecific flu-like symptoms (sweating, shivering, malaise) (Beton et al. 1966). Aside from removing a victim to fresh air and providing supportive medical care, no effective means have been reported for reducing absorption following inhalation exposure to cadmium (Bronstein and Currance 1988; EPA 1989d). Supportive medical care of individuals with inhalation exposure to high levels of cadmium includes monitoring for respiratory distress, assisting ventilation as needed, and administering humidified oxygen (Bronstein and Currance 1988; EPA 1989d). If pulmonary edema develops, individuals may be treated with

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supplemental oxygen, positive-pressure mechanical ventilation, and administration of diuretics, intravenous fluids, and steroid medications. Antibiotic therapy and monitoring fluid balance (due to kidney function impairment) may also be required (Beton et al. 1966; Bronstein and Currance 1988; EPA 1989d; Haddad and Winchester 1990).

Oral exposure to cadmium is not an immediate threat because high doses are irritating enough to induce vomiting. In fact, the only known acute fatalities from oral exposure to cadmium followed intentional ingestion of high doses (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although inducing vomiting is sometimes recommended following ingestion of cadmium (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988), concentrated cadmium solutions may be caustic, and esophageal damage could result from spontaneous or induced vomiting. Administration of water or milk may be indicated for patients able to swallow (Bronstein and Currance 1988; EPA 1989d). Administration of cathartics such as sorbitol or magnesium sulfate to enhance elimination from the gastrointestinal tract has been recommended (EPA 1989d; Stutz and Janusz 1988); however, the administration of activated charcoal to bind unabsorbed cadmium does not appear to be effective (Agency for Toxic Substances and Disease Registry 1990b; Ellenhorn and Barceloux 1988).

The intestinal absorption of cadmium at levels below those leading to gastrointestinal damage is relatively low (5–10% of the administered dose) (Flanagan et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973). Other polyvalent cations including calcium, magnesium, and zinc can interfere with cadmium uptake (Foulkes 1985), but administration of competing cations can in some cases increase rather than decrease cadmium absorption (Jaeger 1990), and is therefore not recommended for the treatment of cadmium ingestion. Oral administration of some compounds that chelate cadmium such as meso-2,3-dimercaptosuccinic acid has been found in rodent studies to reduce absorption following acute oral exposure to cadmium, but other chelators such as dithiocarbamates can increase toxicity (see Section 3.4.1.2). At present, no recommendations for chelation treatment to reduce absorption can be made (Jones and Cherian 1990). Administration of garlic (which is high in reduced sulfhydryl groups) has been shown to decrease oral cadmium toxicity in rats (Cha 1987). Thus, use of garlic could be an area of future research.

Dermal or ocular exposure to high levels of cadmium may cause irritation (Wahlberg 1977) and should be treated by removing contaminated clothing, washing the skin, and thoroughly flushing the eyes (EPA

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1989d; Stutz and Janusz 1988). These measures will also reduce the relatively small potential for dermal absorption of cadmium (see Section 3.4.1.3).

3.11.2 Reducing Body Burden

A variety of chelating agents have been evaluated (Cantilena and Klaassen 1981; Jones et al. 1992, 1994; Kostial et al. 1996; Singh et al. 1996). Some of the more familiar chelators that are beneficial for other toxic metals actually increase cadmium toxicity by mobilizing the cadmium and substantially increasing the renal concentrations and toxicity (Agency for Toxic Substances and Disease Registry 1990b; Goldfrank et al. 1990; Jones and Cherian 1990). One such agent is the chelating agent dimercaprol (also known as BAL, British Anti-Lewisite), commonly used for treating cases of lewisite toxicosis. BAL is widely recognized as harmful in treating cadmium exposures. Some sources recommend using ethylenediamine tetraacetic acid (EDTA) salts (Cantilena and Klaassen 1980, 1981; Ellenhorn and Barceloux 1988; Stutz and Janusz 1988) or use of EDTA with caution about potential nephrotoxicity (EPA 1989d; Haddad and Winchester 1990). Other chelators that have reduced the cadmium burden in animal studies include diethylenetriaminepentaacetic acid (DTPA), 2,3-dimercaptosuccinic acid (DMSA), and various dithiocarbamates (Cantilena and Klaassen 1981, 1982b; Kamenosono et al. 2002a; Wang et al. 1999).

Cantilena and Klaassen (1982a) demonstrated the importance of rapid administration of DTPA, EDTA, or DMSA following acute cadmium exposure if they are to be effective. Waalkes et al. (1983) evaluated the role of metallothionein in the acute drop in chelator efficacy following cadmium poisoning in male Sprague-Dawley rats. Although the chelator, DTPA, reduced cadmium content in the various organs when given immediately after cadmium, it was ineffective at all later times. Increases in hepatic and renal metallothionein did not occur until 2 hours after cadmium, and did not coincide with the earlier drop in chelator efficacy. Blockade of metallothionein synthesis by actinomycin D treatment (1.25 mg/kg, 1 hour before Cd) failed to prolong the chelators effectiveness. Furthermore, newborn rats have high levels of hepatic metallothionein, which had no effect on the time course of chelator effectiveness since DTPA still decreased cadmium organ contents, if given immediately following cadmium, but had no effect if given 2 hours after cadmium. The authors concluded that metallothionein does not have an important role in the acute decrease in efficacy of chelation therapy for cadmium poisoning. The quick onset of chelator ineffectiveness may be due to the rapid uptake of cadmium into tissues, which makes it relatively unavailable of chelation.

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Jones et al. (1992, 1994) investigated a series of monoalkyl and monoalkyl esters of meso-2,3-dimercaptosuccinic acid. Monoisoamyl meso-2,3-dimercaptosuccinate (Mi-ADMS) was an effective chelating agent for reduction of kidney and liver cadmium when administered either parenterally or orally (Jones et al. 1992). This finding was supported by a study by Eybl et al. (1994), which showed that Mi-ADMS, administered orally every 48 hours for 12 days after acute cadmium exposure, was effective at reducing cadmium in the kidney and liver, but not in the testes and brain. Monophenethyl meso-2,3-dimercaptosuccinic acid, mono(3-phenylpropyl) meso-2,3-dimercaptosuccinic acid, and mono(2-phenoxyethyl) meso-2,3-dimercaptosuccinic acid compounds successfully remove “aged” cadmium deposits and can be administered via a variety of routes (Jones et al. 1994).

Another area of chelation therapy research is in the use of multiple chelators. Blaha et al. (1995) evaluated the ability of two carbodithioate chelators, sodium N-(4-methylbenzyl)-4-O-(β -D-galactopyranosyl)-D-glucamine-N-carbodithioate (MeBLDTC) and sodium 4-carboxyamidopiperidine-N-carbothioate (INADTC), singly or in combination to reduce cadmium burden from chronically exposed rats. The combination therapy resulted in a synergistic effect on increased biliary excretion and reduced renal cadmium that, in the case of biliary excretion, was more than doubled that expected for a simple additive interaction.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The toxic effects of cadmium are generally thought to be caused by “free” cadmium ions; that is, cadmium not bound to metallothionein or other proteins (Goyer et al. 1989). However, cadmium bound to metallothionein may have the capacity to directly damage renal tubular membranes during uptake (Suzuki and Cherian 1987). Free cadmium ions may have a number of adverse effects, including inactivation of metal-dependent enzymes, activation of calmodulin, and initiation of the production of active oxygen species (Palmer et al. 1986; Waalkes and Goering 1990).

Respiratory damage caused by acute, high-level inhalation exposure to cadmium can cause impaired lung function that can last many years after exposure (Barnhart and Rosenstock 1984; Townshend 1982). No treatments other than supportive care and avoidance of additional risk factors for lung injury are presently known.

The kidneys appear to be highly vulnerable to chronic cadmium exposure by either the oral or inhalation routes. The basis for the preferential sensitivity of the kidney is related to the filtering and reabsorption of

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circulating cadmium-metallothionein complex, which is then thought to be degraded in the tubular cell lysosomes and released as free intracellular cadmium. The toxic effect results from the limited ability of the kidney to synthesize new cytosolic metallothionein in response to an increasing cadmium load (Goyer et al. 1989). Cadmium bound to metallothionein, however, may also have nephrotoxic activity (Suzuki and Cherian 1987).

No treatments are currently available that specifically target free cadmium ions in the renal cortex, but zinc and calcium can stimulate metallothionein synthesis and may also compete with cadmium for enzyme binding sites. Thus, zinc, and/or calcium supplementation might help reduce renal cadmium toxicity, at least in zinc- or calcium-deficient individuals. It is not known whether administration of these compounds would be beneficial in individuals with adequate zinc and calcium intakes, and their clinical use is not currently recommended. Since one of the postulated mechanisms of cadmium toxicity is the stimulation and production of active oxygen species, it is possible that increasing the cellular levels of antioxidants such as superoxide dismutase, reduced sulfur compounds (particularly glutathione), vitamin C, vitamin E, or β -carotene could reduce renal cadmium toxicity by scavenging active oxygen species prior to reaction with cellular components. Several animal studies have examined co-administration of several antioxidants on cadmium-induced kidney damage. Beneficial effects were found for vitamin E (Shaikh and Tang 1999; Shaikh et al. 1999a), N-acetyl cysteine (Kaplan et al. 2008; Shaikh et al. 1999a, 1999b), glycine (Shaikh and Tang 1999), glycyrrhizin (Nomiya and Nomiya 1998), and a drug containing glycyrrhizin, glycine, and cysteine (Shaikh and Tang 1999; Shaikh et al. 1999a). However, antioxidants are not currently recommended for the treatment of cadmium-exposed humans.

Treatments for the cadmium-related effects on bone have not been evaluated. Although the mechanism of bone damage has not been fully elucidated, it is likely that calcium loss and altered vitamin D metabolism, which result from cadmium-induced kidney damage, play an important role. Thus, treatments that interfere with the renal damage will likely have a beneficial effect on bone.

Research in chelation therapy is promising for agents that can interfere or possibly reverse the toxic effects of cadmium. Xu et al. (1995, 1996) demonstrated that monoisoamyl meso-2,3-dimercapto-succinate, when administered within 1 hour after acute exposure, prevents the formation of cadmium-induced apoptotic DNA fragmentation and associated histopathological injury in the testes of rats. Perry et al. (1989) report a reversal of the cadmium induced hypertension in rats with the chelator d-myo-inositol-1,2,6-triphosphate.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cadmium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cadmium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Cadmium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cadmium are summarized in [Figure 3-6](#). The purpose of this figure is to illustrate the existing information concerning the health effects of cadmium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is a massive database regarding the health effects of cadmium. In humans, the majority of studies have involved workers exposed by inhalation or residents of cadmium-polluted areas exposed primarily in the diet. Quantitative estimates of exposure levels are not available for many of these studies; however, many studies provided information on urinary cadmium levels that would be reflective of the cadmium body burden. Lethality, systemic toxicity, genotoxicity, and cancer have been studied in humans more

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Figure 3-6. Existing Information on Health Effects of Cadmium

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●	●	●	●		●	●		●	●
Dermal		●			●					

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●		●	●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●				●					

Animal

● Existing Studies

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extensively than immunotoxicity or neurotoxicity, with less being known about reproductive or developmental toxicity of cadmium in humans following inhalation or oral exposure. In animals, effects following oral exposures have generally been more thoroughly investigated than those following inhalation exposure, and few studies of cadmium toxicity following dermal exposure in humans were located.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are limited data on the acute toxicity of cadmium in humans. Although there are numerous reports of respiratory effects in workers exposed to high concentrations of cadmium, there are no reliable estimates of levels associated with these effects. Animal studies provide support for identification of the respiratory tract as the most sensitive target of toxicity following inhalation exposure. Acute exposures to high levels of airborne cadmium has resulted in pneumonia, emphysema, and edema in laboratory animals (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; NTP 1995; Palmer et al. 1986) and lower concentrations were associated with focal inflammation and minimal fibrosis (NTP 1995). A decreased immune response in mice was observed at similar cadmium concentrations (Graham et al. 1978; Krzystyniak et al. 1987). Other adverse effects observed at higher concentrations include erosions of the stomach, decreases in body weight, and reduced activity (Rusch et al. 1986). The available acute-duration animal data were considered adequate for derivation of an acute-duration inhalation MRL for cadmium.

There are no reliable human studies on the toxicity of cadmium following acute-duration oral exposure. In laboratory animals, acute exposure to high doses of cadmium resulted in a variety of effects, including altered hematological parameters, focal necrosis and degeneration of the liver, focal necrosis in renal tubular epithelium, necrosis and ulceration in the stomach and intestines, decreased motor activity, and testicular atrophy and necrosis (Andersen et al. 1988; Basinger et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989; Dixon et al. 1976; Kotsonis and Klaassen 1977; Machemer and Lorke 1981; Sakata et al. 1988; Shimizu and Morita 1990). There is some indication that developmental effects (delays in ossification and increased malformations) may occur at lower cadmium doses (Baranski 1985; Machemer and Lorke 1981). The acute-duration oral database was not considered adequate for derivation of an MRL because the results of the study that identified the lowest LOAEL (Baranski 1985) were inadequately reported and were inconsistent with a longer-duration study conducted by the same investigator. Although the data suggest that the developing organism is the most sensitive target,

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additional studies are needed to support this assumption. Studies characterizing the dose-response relationships for the most sensitive effects are needed for derivation of an acute-duration oral MRL.

No reliable information was located regarding toxicity following dermal exposure to cadmium, but based on the lack of reported effects in the workers handling cadmium compounds, it seems unlikely that dermal exposure could deliver a significant dose of cadmium.

Intermediate-Duration Exposure. There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure.

Intermediate-duration inhalation studies in laboratory animals have identified several targets of toxicity including the respiratory tract (Glaser et al. 1986; Kutzman et al. 1986; NTP 1995; Prigge 1978a), reproductive effects (Baranski and Sitarek 1987; NTP 1995), and developing nervous system (Baranski 1984, 1985). At the lowest cadmium concentration tested, alveolar histiocytic infiltration and degeneration or metaplasia in the larynx were observed in mice (NTP 1995) and neurodevelopmental effects were observed in rats (Baranski 1984, 1985). These LOAELs were considered for derivation of an intermediate-duration inhalation MRL; however, an MRL based on the human equivalent concentration of the LOAELs would be lower than the chronic-duration inhalation MRL based on human data. Additional studies are needed to identify no-adverse-effect levels in animals for these sensitive targets of toxicity.

A number of studies have been conducted involving intermediate-duration oral exposure to laboratory animals. The results of these studies suggest that the growing bone is the most sensitive target. The skeletal effects observed in young rats include decreases in bone mineral density, impaired mechanical strength, increased fractures, and increased bone turnover (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b, 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c; Ogoshi et al. 1989). Developmental effects, including impaired renal function and neurodevelopmental alterations, have been observed at similar dose levels (Ali et al. 1986; Baranski et al. 1983; Jacquillet et al. 2007). At higher doses, observed effects included renal damage (proteinuria, tubular necrosis, and decreased renal clearance), liver necrosis, and anemia (Cha 1987; Gatta et al. 1989; Groten et al. 1990; Itokawa et al. 1974; Kawamura et al. 1978; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a), altered immune response (Blakley 1985, 1986; Chopra et al. 1984), decreased motor activity (Kotsonis and Klaassen 1978; Nation et al. 1990), and necrosis and atrophy of seminiferous tubules and decreased sperm count and motility (Cha

1987; Saxena et al. 1989). The database of intermediate-duration animal studies was considered adequate for derivation an intermediate-duration oral MRL based on skeletal effects in growing rats.

No intermediate-duration dermal data were identified in humans or animals. Studies of possible toxicity in animals following intermediate-duration dermal exposure to cadmium are needed to evaluate potential health effects in humans exposed to cadmium primarily by the dermal route.

Chronic-Duration Exposure and Cancer. Data on the chronic toxicity of inhaled cadmium in humans come from numerous occupational exposure studies; no reliable animal studies examining noncancerous end points were identified. These studies have identified the respiratory tract (emphysema, impaired lung function) (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976) and the kidney (tubular proteinuria, decreased glomerular filtration rate, increased excretion of low molecular weight proteins) (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987) as the most sensitive targets of toxicity. Comparisons of the adverse effect levels for these two end points are difficult because the studies on respiratory effects typically reported air concentrations (current levels or estimated cumulative exposure) as the exposure biomarker and those examining renal effects typically used urinary cadmium levels as the exposure biomarker; based on limited data, the kidney appears to be the more sensitive target. Studies examining both end points in occupationally exposed populations would provide valuable information on sensitivity. None of the available human studies were considered adequate for derivation of an inhalation MRL because cadmium air concentrations were poorly characterized or no data were provided on the contribution of dietary cadmium to the cadmium body burden. However, the similarities on the toxicity and toxicokinetics of cadmium following inhalation and oral exposure allow for the use of the oral database to derive an inhalation MRL.

There is an extensive database of studies examining the chronic oral toxicity of cadmium in humans. These environmental exposure studies have identified two sensitive targets of cadmium toxicity—the skeletal system and the kidney. The skeletal effects included increased risk of osteoporosis and bone fractures and decreases in bone mineral density (Alfvén et al. 2000, 2004; Nordberg et al. 2002; Schutte et al. 2008; Staessen et al. 1999; Wang et al. 2003). Renal effects range from death due to renal failure (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006) to increases in the prevalence of low molecular weight proteinuria (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Ishizaki et al. 1989; Izuno et

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al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a; Monzawa et al. 1998; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). Animal studies confirm the identification of the kidney and bone as the most sensitive targets of cadmium toxicity (Akahori et al. 1994; Bernard et al. 1992; Bomhard et al. 1984; Brzóska and Moniuszko-Jakoniuk 2004a, 2004b; Fingerle et al. 1982; Mangler et al. 1988). Sufficient information from human studies is available to derive a chronic oral MRL. No information was located regarding dermal toxicity of chronic cadmium exposure in humans or animals, and studies of dermal toxicity are needed to evaluate risks to populations exposed to cadmium primarily by dermal contact.

The evidence of carcinogenicity from human studies is limited, due to uncertainties in cadmium exposure estimates and confounding factors including exposure to arsenic, a known human lung carcinogen, and smoking. Occupational exposure studies have found significant increases in lung cancer mortalities (Ades and Kazantzis 1988; Järup et al. 1998a; Kazantzis et al. 1988; Stayner et al. 1992a; Sorahan 1987; Sorahan and Waterhouse 1983; Thun et al. 1985). However, lung cancer deaths were often not significantly associated with cadmium exposure or duration. Other studies have not found increases in lung cancer deaths (Armstrong and Kazantzis 1983; Elinder et al. 1985c; Lamm et al. 1992, 1994; Sorahan and Esmen 2004; Sorahan and Lancashire 1997). Additional occupational exposure studies controlling for these exposures and providing more precise cadmium dose estimates are needed to provide more definitive evidence of the carcinogenic potential in humans of inhaled cadmium. Evidence for the carcinogenicity of cadmium by the inhalation route is available from studies in rats (Takenaka et al. 1983). Additional studies in animals are needed to evaluate the lack of an observed increase in lung cancer in mice and hamsters exposed to cadmium by inhalation (Heinrich et al. 1989). Cadmium has not been shown to be carcinogenic following oral exposure in humans (Bako et al. 1982; Hardell et al. 1994; Inskip et al. 1982; Lauwerys and De Wals 1981; Nakagawa et al. 1987; Shigematsu 1984). In rats, however, cadmium increased tumors of the prostate, testes, and hematopoietic system (Waalkes et al. 1992). Additional lifetime-exposure studies in rats, mice, and hamsters orally exposed to cadmium at sufficiently high doses are needed to further define the carcinogenic potential of cadmium.

Genotoxicity. The evidence for the genotoxicity of cadmium is mixed (see [Tables 3-10](#) and [3-11](#)). *In vitro* studies have provided both positive and negative results (Amacher and Paillet 1980; Bruce and Heddle 1979; Casto et al. 1979; Denizeau and Marion 1989; Depault et al. 2006; Fatur et al. 2002; Filipic and Hei 2004; Honma et al. 1999; Jianhua et al. 2006; Lopez-Ortal et al. 1999; Lutzen et al. 2004; Lynn et

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al. 1997; Mikhailova et al. 1997; Oberly et al. 1982; Rozgaj et al. 2002; Shiraishi et al. 1972; Terracio and Nachtigal 1988). Studies of chromosomal aberrations in humans (Bui et al. 1975; Deknuddt and Leonard 1975; Fu et al. 1999; O'Riordan et al. 1978; Tang et al. 1990) and animals (Bruce and Heddle 1979; Desi et al. 2000; DiPaulo and Castro 1979; Fahmy and Aly 2000; Karmakar et al. 1998; Mukherjee et al. 1988a; Tan et al. 1990; Watanabe et al. 1979) exposed to cadmium have also found both positive and negative results. DNA damage has been consistently observed in *in vitro* studies (Devi et al. 2001; Fahmy and Aly 2000; Kasuba et al. 2002; Mukherjee et al. 1988a; Saplakoglu et al. 1997; Valverde et al. 2000; Wronska-Nofer et al. 1999; Zhou et al. 2004b). In animals, parenteral, but not inhalation or oral, cadmium exposure has been found to cause germ cell mutations (Gillivod and Leonard 1975; Suter 1975; Sutou et al. 1980; Watanabe and Endo 1982; Zenick et al. 1982). Additional studies investigating effects in exposed humans using larger populations with quantitative estimates of exposure would be useful to evaluate the human genotoxicity of cadmium.

Reproductive Toxicity. Only limited or conflicting evidence is available to evaluate the potential for cadmium exposure to cause reproductive toxicity in humans. Some studies report no effect on male fertility (Gennart et al. 1992), sex hormone levels (Mason 1990; Menke et al. 2008; Zeng et al. 2004a), sperm density (Noack-Fuller et al. 1993), or semen quality (Jurasović et al. 2004; Saaranen et al. 1989), while others report a reduction in sperm number or viability (Akinloye et al. 2006; Telišman et al. 2000; Xu et al. 1993a) or alterations in sex steroid hormone levels (Akinloye et al. 2006; Jurasović et al. 2004; Telišman et al. 2000). In one study, men occupationally exposed to cadmium at levels resulting in renal damage had no change in testicular function (Mason 1990). Adverse effects in animals from inhalation exposure have been reported including increased duration of the estrous cycle (Baranski and Sitarek 1987; NTP 1995; Tsvetkova 1970), and increased relative testes weight but no loss in reproductive success (Kutzman et al. 1986). Adverse reproductive effects in animals from high-dose, acute, oral cadmium exposure have been reported including testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989), and decreased fertility (Kotsonis and Klaassen 1978; Machemer and Lorke 1981). At lower doses and intermediate exposures, adverse effects have included necrosis and atrophy of seminiferous tubule epithelium (Cha 1987), increased testes weight (Pleasant et al. 1992, 1993), increased prostatic hyperplasias (Waalkes and Rehm 1992), significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, seminiferous tubular damage (Saxena et al. 1989), and decreased fertility (Sutou et al. 1980). Other animal studies for lower dose intermediate exposures, however, report no adverse effects (Baranski et al. 1983; Bomhard et al. 1987; Groten et al. 1990; Kostial et al. 1993; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Pleasants et al. 1992; Pond and Walker 1975; Zenick et al. 1982). Additional studies in animals, as well

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as retrospective, case-matched studies of reproductive success of populations for which occupational or environmental exposure to cadmium has been estimated, are needed to further evaluate the potential reproductive toxicity of cadmium in humans. Additional studies would be useful (preferably with larger sample sizes) to evaluate the robustness of the association between cadmium and adverse effects on sperm.

Developmental Toxicity. The potential for cadmium exposure to cause developmental toxicity from pre- or postnatal exposures in humans is not known. One study in occupationally exposed women reported children with lowered birth weights, but with no increase in malformations (Tsvetkova 1970). However, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight. Many animal studies demonstrate that developmental toxicity may occur following cadmium exposure by oral routes with a relatively few studies reporting developmental effects following inhalation or oral exposure (Ali et al. 1986; Baranski 1985, 1987; Baranski et al. 1983; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Machemer and Lorke 1981; Petering et al. 1979; Pond and Walker 1975; Schroeder and Mitchener 1971; Sorell and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988). At lower inhalation and oral doses, impaired performance on neurobehavioral tests have been observed (Ali et al. 1986; Baranski et al. 1983; Desi et al. 1998; Nagymajtenyi et al. 1997). Retrospective, case-matched studies of developmental toxicity among children of women with known occupational or environmental exposure to cadmium are needed to evaluate the potential for cadmium exposure to cause human developmental toxicity such as skeletal malformations and neurobehavioral effects (as suggested in animal studies). Studies are also needed to follow up on the results of increased susceptibility of young to bone damage (Ogoshi et al. 1989) or suppression of the immune response (Blakley 1985) reported in animals. The difference in the immune response (using the same protocol) between young mice (Blakley 1985) and older mice (Blakley 1988) should also be further evaluated. Studies of postnatal cadmium exposure to children, especially for children with diets deficient in calcium, protein, or iron, would be useful to evaluate whether increased cadmium absorption from the diet leads to developmental effects.

Immunotoxicity. A variety of immunologic effects have been found in animals exposed to cadmium by the oral or inhalation routes (Blakley 1988; Bouley et al. 1984; Cifone et al. 1989a). However, the biological significance of these effects is not clear, and there is little information available on immunotoxicity in humans. Investigations of immunologic function of populations occupationally or environmentally exposed to cadmium, and follow-up mechanistic studies in animals are needed to evaluate the potential immunotoxicity of cadmium exposure in humans.

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Neurotoxicity. A few studies have suggested an association between cadmium exposure in humans and impaired neuropsychologic functioning at levels below those causing nephrotoxicity (Hart et al. 1989b; Marlowe et al. 1985; Thatcher et al. 1982). Neurotoxicity has also been found in animal studies (Nation et al. 1984; Wong and Klaassen 1982). Additional studies to investigate neurologic effects in populations with known cadmium exposure and studies of possible mechanisms of neurotoxicity in animals are needed to evaluate the potential neurotoxicity of cadmium exposure to humans. In addition, studies examining neurobehavioral end points in children would be useful.

Epidemiological and Human Dosimetry Studies. Cause/effect relationships for renal toxicity of cadmium have been derived from studies of workers occupationally exposed to cadmium by inhalation (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985b; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Kawada et al. 1989; Roels et al. 1993; Shaikh et al. 1987; Thun et al. 1989; Toffoletto et al. 1992; Verschoor et al. 1987) and of populations environmentally exposed to cadmium in the diet (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002b; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Roels et al. 1981a; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Suwazono et al. 2000; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Watanabe et al. 2002; Wu et al. 2001; Yamanaka et al. 1998). There is also epidemiological evidence that chronic environmental exposure to cadmium can result in decreases in bone mineral density and increases in the risk of bone fractures and osteoporosis (Åkesson et al. 2005; Alfvén et al. 2000, 2004; Schutte et al. 2008; Staessen et al. 1999). Additional studies are needed to elucidate the mechanisms of these bone effects in humans and to determine if the skeletal system is a more sensitive target of cadmium toxicity than the kidney effects. Measurement of additional toxicity end points (reproductive, developmental, immunological, and neurological) in these well characterized populations are needed to evaluate whether any of these effects may occur at exposure levels below those leading to kidney damage. Additional development of PBPK/PD models is needed to evaluate human exposure scenarios. In its assessment of the U.S. population's exposure to environmental chemicals, the CDC measured urinary cadmium levels. If urinary cadmium levels are monitored in future assessments, it would be useful to also measure biomarkers of tubular dysfunction; these data would be useful in examining possible relationships between cadmium exposure and renal function in the general population.

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Biomarkers of Exposure and Effect.

Exposure. Cadmium levels can be measured in a variety of tissues and fluids, including blood, urine, milk, liver, kidney, hair, and nails (Elinder and Lind 1985; Roels et al. 1981b; Sharma et al. 1982). Blood cadmium is a useful indicator of recent cadmium exposure, and urinary cadmium is a useful indicator of total body burden (Shaikh and Smith 1984). The most important indicator of the potential for toxicological injury is generally considered to be the cadmium concentration in the renal cortex, but individuals vary in the concentration causing renal effects (the "critical concentration") (Roels et al. 1981b). Methods for *in vivo* measurement of cadmium content in the kidney exist, but they are complex and expensive, and involve some exposure to ionizing radiation (Scott and Chettle 1986). Efforts to develop easier, safer, and less costly methods for *in vivo* analysis are needed, as well as studies to determine factors influencing individual variation in critical concentrations. Although many studies correct urinary cadmium levels for creatinine concentration, several investigators (Alessio et al. 1985; Ikeda et al. 2003a; Moriguchi et al. 2005b) have questioned the validity of this approach due to wide intra- and interindividual variability and age-related decline in levels. Additional studies are needed to further investigate methods to account for dilution in urine spot samples.

Effect. A number of sensitive tests are available to detect early stages of renal dysfunction that are known to be caused by cadmium exposure. These include analysis of urinary excretion of β_2 -microglobulin, retinol-binding protein, metallothionein, or enzymes (Shaikh and Smith 1984). However, renal damage detected by these tests is not necessarily associated with cadmium exposure. Additional studies are needed to evaluate current or potentially new urinary or serum biomarkers in cadmium-exposed populations and their association with incipient injury to the kidney caused by cadmium. The bone is a sensitive target of cadmium toxicity, particularly during growth and in the elderly; studies are needed to develop sensitive biomarkers to detect early signs of bone damage.

Absorption, Distribution, Metabolism, and Excretion. Good information exists on cadmium toxicokinetics in humans and animals. PBPK/PD models have been developed to predict the critical organ dose as a function of route, duration, and level of exposure by the inhalation and oral routes (Kjellström and Nordberg 1978, 1985). Although general factors influencing absorption, distribution, metabolism, and excretion are known, additional studies are needed to provide information on metal metabolism and interactions that support quantitative evaluation of individual variations and resulting differences in renal cadmium accumulation. Very limited information exists on the dermal absorption of

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cadmium (Skog and Wahlberg 1964; Wester et al. 1992). Additional studies on the dermal absorption of cadmium are needed.

Comparative Toxicokinetics. Animal and human studies have generally reported comparable toxicokinetics of cadmium (Kjellström and Nordberg 1985; Nordberg et al. 1985), suggesting that rats, mice, and rabbits are suitable models for cadmium toxicity in humans. However, some concerns have been raised about the appropriateness of the rat model for cadmium-induced lung tumors in humans because of differences in the morphology of the rat respiratory tract and resulting differences in cadmium particle deposition patterns and target cell populations. This is especially of concern because cadmium appears to be a contact carcinogen for lung cancer. Additional studies on the differences between the rat and human clearance rates, speciation at the level of the target cell, and protein transporters (as they relate to solubility and susceptibility) are needed to evaluate the appropriateness of the rat model for predicting cadmium-induced human lung cancers. Additional studies on differences in species, strain, sex, age, and other factors on cadmium kinetics and carcinogenic or other systemic effects are also needed to extrapolate the animal data to potential human toxicity. Additional studies establishing the toxicokinetics of cadmium in pregnant animals are needed to assess the relevance of the developmental effects observed in animals.

Methods for Reducing Toxic Effects. The mechanisms of cadmium absorption across epithelial layers are likely to be via nonspecific mechanisms (Foulkes 1989). No methods are known for influencing absorption across the lung, but absorption across the gastrointestinal tract may be influenced by dietary status (Flanagan et al. 1978). Studies to determine whether dietary adjustments might help decrease cadmium uptake from food or water are needed. Studies to determine the effects of dietary deficiencies in calcium are needed to further evaluate the risk of cadmium exposure to susceptible populations. Uptake across the skin is probably sufficiently slow that simple washing of exposed areas is adequate to prevent excessive absorption (Skog and Wahlberg 1964).

Once cadmium is absorbed, it tends to accumulate in the kidney, which is the main target tissue for chronic low-dose exposure. The cellular and molecular basis for the preferential accumulation in the kidney is only partially understood (Waalkes and Goering 1990), and additional studies to define the rate-limiting steps in renal uptake and renal clearance of cadmium are needed to design strategies for reducing the rate of cadmium accumulation in this tissue. Additional studies on existing and new chelating agents and different treatment regimens are needed to improve the clinical therapies for acute and chronic exposures to cadmium.

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The mechanism of cadmium toxicity in renal cells and other tissues probably involves binding of free cadmium ions to key cellular enzymes and proteins (Waalkes and Goering 1990). Thus, any agent that prevents cadmium from binding might help prevent toxicity. The endogenous cadmium-binding protein can serve this function; however, metallothionein-cadmium complexes may have renal toxicity (Suzuki and Cherian 1987). Additional studies on the role of metallothionein in cadmium toxicity would be useful. Additional studies are needed on alternative substrate molecules or drugs that could interact with free cadmium and prevent binding to key cellular enzymes, as well as the ability of antioxidants to reduce damage from active-oxygen species produced by cadmium in tissues.

The impaired renal function that is the typical adverse effect of excessive cadmium exposure is neither clinically treatable nor reversible (Agency for Toxic Substances and Disease Registry 1990b; Roels et al. 1989). Studies on potential supportive treatment or remedies for cadmium-induced mild renal impairment would be valuable.

The bone is also a sensitive target of cadmium toxicity; however, methods for the treatment of the observed effects, decreased bone mineral density and increased fractures, have not been developed and are needed.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There is limited information on the toxicity of cadmium in children. Although it is likely that children will have similar effects as adults, there is some suggestive evidence that childhood exposure may result in increased renal toxicity, as compared to persons only exposed as adults (Trzcinka-Ochocka et al. 2004). Additionally, studies in animals suggest that young animals are more susceptible to cadmium-induced bone damage than adults (Ogoshi et al. 1989); this has not been investigated in humans. Studies are needed to evaluate whether there are age-specific differences in the toxicity of cadmium in humans. As discussed in the Developmental Toxicity section above, there are limited data on the developmental toxicity of cadmium in humans, particularly potential neurodevelopmental effects and additional studies are needed.

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Additional research is needed on the toxicokinetics of cadmium during long-term, low-level exposures to determine the potential long-term tissue burdens that are likely to result especially for the susceptible tissues of liver, kidney, and bone. Data in animals suggest that children may absorb more cadmium than adults, but there are no human data examining these potential differences in the toxicokinetic properties of cadmium. Additional information is needed on cadmium transport across the blood-brain barrier in the developing fetus, and the role of metallothionein in the placenta.

Neurological and behavioral studies are needed that use the more sophisticated measures available today to evaluate children for *in utero*, acute, and longer term exposures. These studies should have the appropriate controls for confounding factors such as lead, parental use of ethanol, and living conditions.

Additional studies are needed to evaluate whether or not biomarkers of cadmium exposure and effects that have been developed for adults are also applicable to children. If not, new biomarkers of exposure and effect need to be developed.

The effects of nutritional status (iron, zinc, and calcium levels) on cadmium absorption and accumulation in children need further evaluation. Improved regimens and choices for chelation therapy are also needed.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A number of research projects are in progress investigating the health effects of cadmium. These projects are summarized in [Table 3-14](#).

3. HEALTH EFFECTS

Table 3-14. Ongoing Studies on Cadmium

Investigator	Study topic	Institution	Sponsor
Fadrowski, J	Determination if environmental cadmium exposure is associated with chronic kidney disease in children	John Hopkins University	National Institute of Environmental Health Sciences
Nebert, DW	Identify and characterize genes responsible for interindividual differences in the response to cadmium	University of Cincinnati	National Institute of Environmental Health Sciences
Thomas, DG and Kennedy, TS	Examination of the possible association between cadmium levels in maternal blood and breast milk and cognitive development in infants	Oklahoma State University	National Research Initiative
Newcomb, PA	Examination of the possible association between cadmium exposure and risk of breast cancer	Fred Hutchinson Cancer Research Center	National Institute of Environmental Health Sciences
Louie, MC	Examination of the contribution of cadmium to the progression of breast cancer	Dominican University of California	National Cancer Institute
Meliker, JR	Examination of possible association between cadmium exposure and breast cancer risk	State University of New York, Stony Brook	National Institute of Environmental Health Sciences
Rull, RP	Examination of possible association between cadmium exposure and endometrial cancer risk	Northern California Cancer	National Institute of Environmental Health Sciences
El Mauayed, M	Examination of the possible association between cadmium exposure and diabetes risk in carriers of a genetic variation of the zinc transporter ZnT8	Northwestern University	National Institute of Environmental Health Sciences
Guallar, EO	Possible association between cadmium exposure and cardiovascular risk in children	Johns Hopkins University	National Institute of Environmental Health Sciences
Heggland, SJ	Mechanisms of cadmium-induced osteotoxicity	Albertson College of Idaho	National Institute of Environmental Health Sciences

Source: FEDRIP 2012

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists the common synonyms, trade names, and other pertinent identification information for cadmium and its most important compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of cadmium and its most important compounds.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Cadmium and Compounds^a

Characteristic	Information		
Chemical name	Cadmium	Cadmium carbonate	Cadmium chloride
Synonym(s)	Colloidal cadmium	Otavite ^b ; cadmium monocarbonate; carbonic acid; cadmium salt	Caddy ^b ; Vi-Cad ^b ; cadmium dichloride; dichlorocadmium
Registered trade name(s)	No data	No data	No data
Chemical formula	Cd ^b	CdCO ₃ ^b	CdCl ₂ ^b
Chemical structure	Cd ^b	CdCO ₃ ^b	CdCl ₂ ^b
Identification numbers:			
CAS registry	7440-43-9 ^b	513-78-0 ^b	10108-64-2
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	D006	D006	D006
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	NA2570/IMCO 6.1
HSDB	282	1612	278
NCI	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Cadmium and Compounds^a

Characteristic	Information		
Chemical name	Cadmium oxide	Cadmium sulfate	Cadmium sulfide
Synonym(s)	Aska-Rid ^b ; cadmium fume; cadmium monoxide	Cadmium sulphate; sulfuric acid; cadmium (2+) salt	Cadmium monosulfide; cadmium yellow; cadmium orange; cadmopur yellow; greenockite ^b ; capsebon ^b
Registered trade name(s)	No data	No data	No data
Chemical formula	CdO ^b	CdSO ₄ ^b	CdS ^b
Chemical structure	CdO ^b	CdSO ₄ ^b	CdS ^b
Identification numbers:			
CAS registry	1306-19-0 ^b	10124-36-4 ^b	1306-23-6 ^b
NIOSH RTECS	No data	No data	No data
EPA hazardous waste	D006	D006	D006
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN2570/IMCO 6.1	No data	No data
HSDB	1613	274	1614
NCI	No data	No data	No data

^aAll information obtained from HSDB 2008 except where noted.^bO'Neil et al. 2006.

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Cadmium and Compounds^a

Property	Cadmium	Cadmium carbonate
Molecular weight	112.41 ^b	172.42 ^b
Color	Silver-white ^b	White ^c
Physical state	Lustrous metal ^b	Powder or rhombohedral leaflets ^b
Melting point	321 °C ^b	Decomposes at 357 °C
Boiling point	765 °C ^b	No data
Density at 20 °C	8.65 g/cm ³ at 25 °C ^b	4.58 g/cm ^{3f}
Odor	Odorless	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 20 °C	Insoluble ^b	Insoluble ^f
Organic solvents	Acids, NH ₄ NO ₃ ^f	Acids, especially HNO ₃ , concentrated NH ₄ solution ^c
Partition coefficients:		
Log K _{ow}	No data	No data
Log K _{oc}	No data	No data
Vapor pressure	7.5x10 ⁻³ mmHg at 257 °C	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	250 °C	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Cadmium and Compounds^a

Property	Cadmium chloride	Cadmium oxide
Molecular weight	183.32	128.41 ^b
Color	White ^c	Dark brown ^b
Physical state	Rhombohedral crystals ^b	Infusible powder or cubic crystals ^b
Melting point	568 °C ^b	Decomposes at 950 °C
Boiling point	960 °C ^b	Decomposes at 950 °C
Density at 20 °C	4.047g/cm ³ at 25 °C ^e	Crystals 8.15 g/cm ³ ; amorphous powder 6.95 g/cm ^{3c}
Odor	Odorless ^c	Odorless
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 20 °C	Soluble ^b	Insoluble ^b
Organic solvents	Acetone, slightly soluble in MEOH and ETOH ^b	Dilute acid, slowly soluble in NH ₄ salts ^b
Partition coefficients:		
Log K _{ow}	No data	No data
Log K _{oc}	No data	No data
Vapor pressure	10 mmHg at 656 °C ^e , 40 mmHg at 736 °C ^d , 760 mmHg at 967 °C ^d	1 mmHg at 1,000 °C ^e ; 10 mm Hg at 1149 °C; 40 mm Hg at 1257 °C
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Cadmium and Compounds^a

Property	Cadmium sulfate	Cadmium sulfide
Molecular weight	208.47 ^b	144.48 ^b
Color	Colorless ^c	Light yellow or orange ^b ; brown ^c
Physical state	Monoclinic crystals (hydrate) ^b	Cubic or hexagonal structure ^b
Melting point	1,000 °C ^c	1,750 °C ^c
Boiling point	No data	Sublimes in N ₂ at 980 °C ^c
Density at 20 °C	4.69 g/cm ^{3b}	4.82 g/cm ³ , hexagonal structure ^b , 4.5 g/cm ³ , cubic structure ^b
Odor	Odorless	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 20 °C	Soluble ^c	Soluble at 1.3 mg/L at 18 °C ^b
Organic solvents	Insoluble in alcohol ^c , acetone, ammonia ^f	Concentrated or warm dilute mineral acids ^b
Partition coefficients:		
Log K _{ow}	No data	No data
Log K _{oc}	No data	No data
Vapor pressure at 20 °C	No data	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

^aAll information from HSDB 2008, except where noted.^bO'Neil et al. 2006.^cSax and Lewis 2001.^dFarnsworth 1980.^eSax and Lewis 2000.^fLide 2005.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Cadmium is a widely but sparsely distributed element found in the earth's crust at concentrations ranging from 0.1 to 5 ppm, primarily as sulfide minerals in association with zinc ores, zinc-bearing lead ores, and or complex copper-lead-zinc ores (Morrow 2001). Approximately 3 kg of cadmium for each ton of zinc are produced (OECD 1995). About 80% of cadmium production is associated with zinc production, while the other 20% is associated with lead and copper byproduct production and the recapture of cadmium from finished products (Morrow 2001). Between 2003 and 2006, the annual cadmium refinery production in the United States declined from 1,450 to 700 metric tons, dropping 52% between 2005 and 2006 (USGS 2007, 2008). Demand for cadmium in the nickel-cadmium (Ni-Cd) battery industry is strengthening as demand in other areas, like coatings and pigments, has been decreasing due to environmental concerns and regulations. Despite this demand, primary production of cadmium may decrease as zinc prices increase, since producers may choose to discard the cadmium byproduct instead of refining it (USGS 2008).

One company produced primary cadmium in the United States during 2007: Clarksville (Zinifex Ltd.), Clarksville, Tennessee. The Big River Zinc Corporation (Korea Zinc Co, Ltd), Sauget, Illinois operation was closed in 2006, citing mine closures and the increasing price of zinc concentrate (USGS 2008). In June 2006, it was purchased by ZincOx Resources plc, Surrey, United Kingdom (USGS 2007). A third company in Ellwood, Pennsylvania, International Metals Reclamation Co. Inc. (INMETCO), recovers cadmium from spent nickel-cadmium batteries, which began reclaiming cadmium in 1995 (USGS 2007). In 2005, it was estimated that the total cadmium recovery rate was only 12%, with an estimated 40,000 tons of cadmium being disposed of in municipal waste or held in household storage or industry stockpiles between 1996 and 2005 (USGS 2007).

The following companies are currently cited as major producers of cadmium compounds: GFS Chemicals Inc., Columbus, Ohio (cadmium chloride, cadmium sulfate); CERAC Inc., Milwaukee, Wisconsin (cadmium sulfide); and EP Scientific Products, LLC (cadmium sulfide) (SRI 2007). BASF Catalysts LLC, Louisville, Kentucky was specifically cited as a major producer of cadmium sulfide/sulfoselenide pigments (SRI 2007).

Tables 5-1 and 5-2 list the facilities in each state that manufacture or process cadmium and cadmium compounds, respectively, the intended use, and the range of maximum amounts stored on site. The data

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Cadmium

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	19	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	14	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14
AZ	12	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13
CA	41	0	99,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	8	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 12
CT	5	0	99,999	7, 8, 10, 11
FL	6	0	99,999	1, 2, 3, 4, 6, 7, 8, 10, 12
GA	8	0	999,999	1, 3, 6, 8, 13, 14
IA	9	0	99,999	1, 5, 7, 8, 12, 13
ID	6	10,000	999,999	1, 3, 5, 12, 13
IL	25	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14
IN	10	0	999,999	1, 2, 5, 7, 8, 9, 10, 12
KS	6	100	99,999	1, 3, 7, 8, 12
KY	11	0	999,999	1, 2, 3, 5, 6, 7, 8, 11
LA	7	0	999,999	1, 3, 5, 6, 8, 10, 12, 13
MA	13	0	99,999	1, 2, 3, 4, 7, 8, 10
MD	5	100	49,999,999	1, 2, 4, 5, 6, 13
MI	19	0	99,999	1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14
MN	10	0	999,999	1, 3, 4, 7, 8, 9, 10, 11, 12, 13
MO	7	0	999,999	1, 2, 3, 4, 5, 6, 8, 14
MS	7	0	9,999	5, 7, 8, 12
NC	13	0	9,999,999	1, 5, 7, 8, 9, 10, 12, 14
NE	9	100	99,999	1, 2, 5, 7, 8, 12
NH	4	0	999	1, 3, 8, 12
NJ	18	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NV	2	10,000	99,999	1, 2, 3, 5, 12, 13
NY	21	0	9,999,999	2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14
OH	32	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	16	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
OR	7	0	9,999,999	1, 5, 8, 12
PA	35	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	1	0	99	8
RI	4	0	9,999	2, 3, 7, 8
SC	20	0	9,999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12
TN	17	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
TX	28	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
UT	8	0	99,999	1, 5, 6, 7, 8, 12, 13

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Cadmium

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
VA	12	0	99,999	1, 5, 7, 8, 9, 10, 11, 13
WA	5	0	9,999	1, 2, 3, 5, 10, 13
WI	14	0	49,999,999	3, 7, 8, 10, 11, 12
WV	3	100	99,999	7, 8, 12
WY	1	0	99	1, 13

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI09 2011 (Data are from 2009)

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Cadmium Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	14	0	499,999,999	1, 5, 7, 9, 11, 12, 14
AL	31	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
AR	19	100	999,999	1, 2, 3, 5, 7, 8, 12, 13, 14
AZ	30	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 12, 13, 14
CA	28	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	10	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CT	28	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
DE	2	100	9,999	1, 5
FL	11	0	999,999	1, 2, 3, 5, 6, 8, 12, 13, 14
GA	15	0	999,999	1, 2, 3, 5, 6, 7, 8, 13
IA	5	0	99,999	1, 5, 7, 8, 9, 12
ID	14	100	9,999,999	1, 5, 6, 7, 11, 12, 13, 14
IL	46	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
IN	19	0	999,999	1, 5, 7, 8, 13, 14
KS	7	0	99,999	1, 7, 8, 11, 13
KY	19	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 12, 13
LA	12	0	999,999	1, 2, 3, 5, 7, 8, 12, 13
MA	14	0	999,999	1, 3, 4, 5, 6, 7, 8, 12, 13
MD	9	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 13
MI	24	0	99,999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 13
MN	10	100	999,999	1, 5, 7, 8, 9, 13
MO	14	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 13
MS	9	0	999,999	1, 5, 7, 8, 12
MT	3	1,000	9,999,999	1, 2, 3, 4, 5, 6, 13
NC	14	0	49,999,999	1, 7, 8, 13
NE	8	1,000	999,999	1, 2, 5, 8, 12, 13, 14
NH	1	1,000	9,999	7, 10
NJ	35	0	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 12
NM	6	1,000	9,999,999	1, 5, 13
NV	22	100	49,999,999	1, 2, 3, 5, 6, 7, 9, 10, 12, 13, 14
NY	26	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
OH	82	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	19	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
OR	4	100	99,999	1, 5, 8
PA	67	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
PR	1	100	999	8

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Cadmium Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
RI	8	100	99,999	2, 3, 7, 8, 11
SC	18	0	999,999	1, 4, 5, 6, 7, 8, 11, 12, 13, 14
TN	35	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14
TX	36	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
UT	15	1,000	49,999,999	1, 5, 6, 7, 8, 12, 13
VA	11	0	99,999	1, 5, 7, 8, 12, 14
WA	17	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14
WI	14	100	49,999,999	1, 3, 5, 7, 8, 10, 11, 12
WV	8	0	999,999	1, 2, 3, 7, 8, 11, 12, 13

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI09 2011 (Data are from 2009)

listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI) (TRI09 2011). Because only certain types of facilities were required to report, this is not an exhaustive list.

Cadmium metal is available in purities ranging from 99.5 to 99.999% in the following grades: technical, powder, pure sticks, ingots, slabs, and high-purity crystals (<10 ppm impurities) (HSDB 2008).

Cadmium (as cadmium oxide) is obtained mainly as a byproduct during the processing of zinc-bearing ores (e.g., sphalerites), and also from the refining of lead and copper from sulfide ores (e.g., galena) (Morrow 2001). Cadmium oxide produced during roasting of ores is reduced with coke, and cadmium metal is separated by distillation or electrodeposition (Elinder 1985a). Commercial-grade cadmium oxide is available in purities ranging from 99 to 99.9999%; common impurities are lead and thallium (NTP 2005). Cadmium chloride is produced by reacting molten cadmium with chlorine gas at 600 °C or by dissolving cadmium metal or the oxide, carbonate, sulfide, or hydroxide in hydrochloric acid and subsequently vaporizing the solution to produce a hydrated crystal (HSDB 2008; IARC 1993). In preparing the anhydrous cadmium chloride salt, the hydrate is refluxed with thionyl chloride or calcined in a hydrogen chloride atmosphere (HSDB 2008). Commercial cadmium chloride is available as a hydrate mixture with a purity range of 95.0–99.999% (NTP 2005).

The commercial preparation of cadmium sulfate usually involves dissolution of the metal oxide, carbonate, or sulfide in sulfuric acid with subsequent cooling or evaporation (HSDB 2008). Anhydrous cadmium sulfate is prepared by oxidation of the sulfide or sulfite at elevated temperatures (Herron 2003); or by melting cadmium with ammonium or sodium peroxodisulfate (Schulte-Schrepping and Piscator 2002). Cadmium sulfate monohydrate, which is the cadmium compound most often marketed, is produced by evaporating a cadmium sulfate solution above 41.5 °C (Schulte-Schrepping and Piscator 2002). Cadmium sulfate is available in technical and C.P. (chemically pure) grades (Lewis 2001). Cadmium sulfide can be prepared by a direct reaction with hydrogen sulfide and cadmium vapor or between sulfur and cadmium metal or cadmium oxide (Herron 2003). Cadmium sulfide is available in technical, N.F. (national formulary grade), and high-purity (single crystals) (Lewis 2001). Cadmium carbonate is produced by heating an acidified solution of cadmium chloride and urea in a sealed tube at 200 °C, the slow absorption of carbon dioxide to cadmium oxide, or the precipitation of the hemihydrate from reaction of ammonium carbonate in cadmium ion solution (Herron 2003).

5.2 IMPORT/EXPORT

Imports of cadmium into the United States declined steadily from 1994 through 1998, dropping from 1,110 metric tons per year to an estimated 650 metric tons in 1998 (USGS 1999). In 1986, imports of cadmium metal for consumption increased significantly to 3,000 metric tons, but continually decreased into the 1990s. From 2003 to 2005, cadmium imports of metal, alloys, and scrap increased from 112 to 288 tons, 74–207 tons of which were metal-only imports (USGS 2008). Cadmium imports peaked in 2005 and then declined through 2007, with 172 tons of cadmium metal only and 174 tons of metal, alloys, and scrap imported (USGS 2008). The principal supplying countries were Australia (41%), Canada (20%), China (10%), and Peru (9%) (USGS 2008).

In the mid-1990s, exports varied widely from 38 metric tons in 1993, to 1,450 metric tons in 1994, to 550 metric tons in 1997. In 2003, cadmium exports (reported as metal, alloys, and scraps) were 615 tons, with exports decreasing to only 154 tons the following year (USGS 2008). Exports surged again in 2005 to 686 tons, but have since been steadily decreasing from 483 tons in 2006 to 304 tons in 2007 (USGS 2008).

5.3 USE

Cadmium, its alloys, and its compounds are used in a variety of consumer and industrial materials. The dominant use of cadmium is in active electrode materials in Ni-Cd batteries (83% of total cadmium use) (USGS 2008). Cadmium demand for other uses such as pigments for plastics, ceramics, and glasses; stabilizers for polyvinyl chloride (PVC) against heat and light; engineering coatings on steel and some nonferrous metals; and components of various specialized alloys have been decreasing. (Elinder 1992; IARC 1993; Thornton 1992; USGS 2008). Cadmium salts have been used in a limited capacity as a fungicide for golf courses and home lawns (EPA 2006b). Cadmium chloride is used in photography, photocopying, dyeing, calico printing, vacuum tube manufacture, pigment manufacture, galvanoplasty, lubricants, ice-nucleation agents, and in the manufacture of special mirrors (Herron 2003). However, the significance of cadmium chloride as a commercial product is declining (IARC 1993).

Cadmium-based colorants are used mainly in engineering plastics, ceramics, glasses, and enamels (IARC 1993; OECD 1995). Cadmium sulfide is especially important in this industry, especially in glasses and plastics; however, environmental and health concerns have contributed to a decrease in its production (Herron 2003). Cadmium sulfide (yellow) and cadmium selenide (red) are combined to create solid C.P. toners ranging in color from yellows and oranges to reds and maroons (Herron 2003). Cadmium

sulfide and cadmium telluride are used in solar cells and a variety of electronic devices which depend on cadmium's semiconducting properties (Herron 2003; IARC 1993; OECD 1995). The photoconductive and electroluminescent properties of cadmium sulfide have been applied in manufacturing a variety of consumer goods (IARC 1993). Cadmium sulfate solution is used in standard Weston cells (Herron 2003).

Though cadmium metal consumption for batteries has grown steadily since the 1980s and currently consumes 83% of the cadmium produced, other uses of cadmium began declining in the mid 1990s. Pigment, stabilizer, coating, and alloy markets for cadmium are decreasing due to environmental concerns (USGS 1997, 2008). Proposed legislation, particularly in the European Union, restricting cadmium in consumer products may have a negative effect on cadmium demand (USGS 2008). Excessive exports from Bulgaria and Russia in 1997 caused a drop in the average price of cadmium from \$1.84 per pound in 1995 to \$0.51 per pound in 1997. Also, Ni-Cd batteries have been replaced in some markets by lithium-ion and nickel metal hydride batteries (USGS 2008). As of 2006, Ni-Cd batteries made up 18% of the rechargeable battery market, down from 56% in 1996 with global sales decreasing 16% between 2005 and 2006 (USGS 2008). Despite this trend, demand for cadmium may increase due to new market opportunities for Ni-Cd batteries (USGS 2008). Regulations by local authorities have forced the recycling of cadmium in Ni-Cd batteries, further depressing the demand for primary cadmium metal (USGS 1999).

5.4 DISPOSAL

Cadmium-containing wastes are subject to regulations concerning their treatment, storage, and disposal (see Chapter 8) (EPA 1982a; HSDB 2008; U.S. Bureau of Mines 1990). In many states, the disposal of Ni-Cd batteries as municipal waste is prohibited (USGS 2007). Incineration of municipal wastes, particularly from older, poorly controlled facilities, is a potential environmental source of cadmium. In modern incineration plants, about 99.9% of cadmium was captured in boilers and control equipment (OECD 1995).

A range of physicochemical processes is available for treatment of cadmium in liquid waste process streams, including ion exchange, electrolysis, cementation, and adsorption. Both ion exchange and sulfide precipitation are used as alternate processes aimed at achieving low cadmium residuals in liquid wastes (UN 1985). Combining processes, for example, conducting the primary precipitation of cadmium as hydroxide followed by secondary precipitation of residual cadmium as sulfide, has also been adopted. The more general application of the sulfide precipitation technique, however, is constrained due to a

tendency for formation of colloidal precipitate, the toxicity and odor of hydrogen sulfide, and the necessity to oxidize residual sulfide occurring in emissions prior to discharge (UN 1985).

The most widely used treatment process involves the alkaline precipitation of cadmium as hydroxide or basic salts (UN 1985). Removal of specific metal species during hydroxide precipitation is pH-dependent, and some components of the waste stream can influence the solubility of cadmium hydroxide. After filtration, the sludge formed from the conversion of soluble cadmium compounds to insoluble compounds can be deposited in a suitable landfill (UN 1985).

Various cadmium-bearing wastes are subject to aggressive leaching in refuse media, particularly under aerobic conditions (UN 1985). While liquid wastes are banned from land disposal, the leaching tendency is accentuated in the presence of brine solutions. Also, the mobility of cadmium in landfill conditions could be enhanced in the presence of mineral acids, which tend to solubilize cadmium compounds, or amine-containing materials, which tend to complex cadmium ions. Waste containing mineral acids, cyanides, organic solvents, and amine-type substances should not be landfilled near cadmium-bearing wastes (UN 1985).

In the laboratory, a recommended method for recovering cadmium from small quantities of cadmium oxide wastes uses a minimum amount of concentrated nitric acid to form nitrates. The solution is evaporated in a hood to form a thin paste, and then diluted with water and saturated with hydrogen sulfide. After the filtration, the precipitate is washed, dried, and returned to the supplier (UN 1985).

Cadmium recovery from scrap metals and batteries is becoming increasingly popular, with the main emphasis being on recycling Ni-Cd batteries (Morrow 2001). Battery recycling is relatively easy and can be achieved using pyrometallurgical (high temperature) or hydrometallurgical (wet chemical) processes (Morrow 2001). In these processes, the metallic waste that contains iron, nickel, cadmium, and their oxides and hydroxides are separated from the other battery components and then converted back to a metal that has a technical purity required for the production of new batteries (Morrow 2001). Cadmium-based coatings can be recycled using electric-arc furnace (EAF) dust, which is obtained through the re-melting of scrap steel that contains cadmium coatings and cadmium impurities (Morrow 2001). INMETCO in Ellwood, Pennsylvania recovers cadmium from spent Ni-Cd batteries, and has developed several collection programs to help facilitate battery recycling (USGS 2007). Although participation in battery recycling has increased in businesses, communities, and retailers, the total recovery of cadmium in 2005 was only 12% (USGS 2007).

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

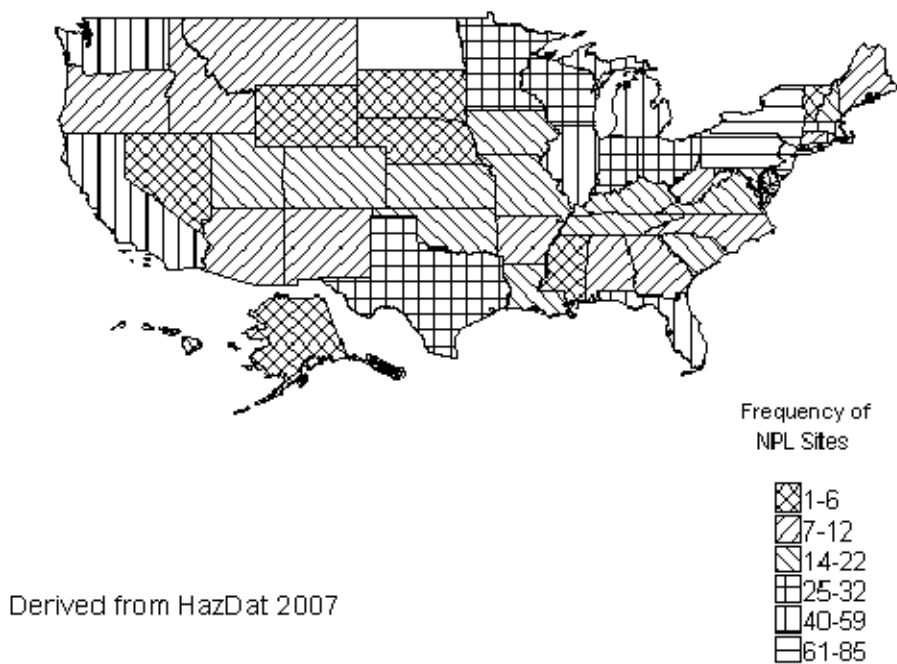
Cadmium has been identified in at least 1,014 of the 1,669 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). Cadmium compounds have been identified in at least 3 of the 1,669 hazardous waste sites. However, the number of sites evaluated for cadmium is not known. The frequency of these sites can be seen in [Figures 6-1 and 6-2](#). Of the 1,014 sites where cadmium has been identified, 1,005 are located within the United States, 6 are located in the Commonwealth of Puerto Rico (not shown), 2 are located in Guam, and 1 is located in the Virgin Islands. All sites where cadmium compounds were detected are located in the United States.

Cadmium occurs in the earth's crust at an abundance of 0.1–0.5 ppm and is commonly associated with zinc, lead, and copper ores. It is also a natural constituent of ocean water, with average levels between <5 and 110 ng/L; with higher levels reported near coastal areas and in marine phosphates and phosphorites (Morrow 2001). Natural emissions of cadmium to the environment can result from volcanic eruptions, forest fires, generation of sea salt aerosols, or other natural phenomena (EPA 1985a; Morrow 2001; Shevchenko et al. 2003). Cadmium is refined and consumed for use in batteries (83%), pigments (8%), coatings and platings (7%), stabilizers for plastics (1.2%), and nonferrous alloys, photovoltaic devices, and other (0.8%) (USGS 2008). Nonferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of cadmium in the environment.

Cadmium can be released to the atmosphere through metal production activities, fossil fuel combustion, and waste incineration. The main cadmium compounds found in air are cadmium oxide, chloride, and sulfate, and these compounds are expected to undergo minimal transformation in the atmosphere (EPA 1980d). The major fate of cadmium in air is through transport and deposition. Cadmium can travel long distances in the atmosphere and then deposit (wet or dry) onto surface soils and water, which can result in elevated cadmium levels even in remote locations (Shevchenko et al. 2003). Results from the 2006 final report of EPA's Urban Air Toxic Monitoring program reported average daily cadmium levels of <0.01 µg/m³ at several monitoring sites throughout the United States (EPA 2007). These sites include: Bountiful, Utah; Northbrook, Illinois; Austin, Texas; St. Louis, Missouri; Indianapolis, Indiana; and Birmingham, Alabama (EPA 2007). Atmospheric concentrations of cadmium are generally highest in the vicinity of cadmium-emitting industries (Elinder 1985a; Pirrone et al. 1996). Due to advances in pollution control technology, cadmium emissions to air are not expected to increase, even though

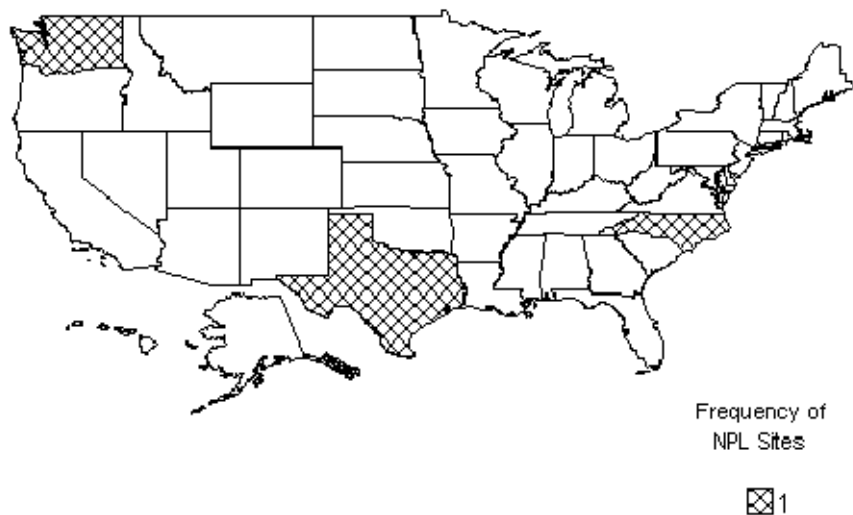
6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with Cadmium Contamination



6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-2. Frequency of NPL Sites with Cadmium Compounds Contamination



Derived from HazDat 2007

6. POTENTIAL FOR HUMAN EXPOSURE

cadmium-emitting industries are expected to grow (Herron 2003; Morrow 2010; Schulte-Schrepping and Piscator 2002). Except for those who live near cadmium-emitting industries, inhalation of cadmium in the ambient air is not a major source of exposure.

The main sources of cadmium to soil include atmospheric deposition and direct application methods such as phosphate fertilizer use and sewage sludge disposal. Some phosphate fertilizers can contain up to 300 mg Cd/kg (Alloway and Steinnes 1999). Wet and dry deposition of cadmium from the atmosphere may also contribute sizable amounts of cadmium to soil in the areas surrounding sources of atmospheric emissions (EPA 1985a; Mielke et al. 1991). Cadmium's mobility in soil depends on several factors including the pH of the soil and the availability of organic matter. Generally, cadmium will bind strongly to organic matter and this will, for the most part, immobilize cadmium (Autier and White 2004). However, immobilized cadmium is available to plant life and can easily enter the food supply. Cadmium in soil tends to be more available when the soil pH is low (acidic) (Elinder 1992).

Water sources near cadmium-emitting industries, both with historic and current operations, have shown a marked elevation of cadmium in water sediments and aquatic organisms (Angelo et al. 2007; Arnason and Fletcher 2003; Brumbaugh et al. 2005; Mason et al. 2000; Paulson 1997). In surface water and groundwater, cadmium can exist as the hydrated ion or as ionic complexes with other inorganic or organic substances. While soluble forms may migrate in water, cadmium is relatively nonmobile in insoluble complexes or adsorbed to sediments. Cadmium is taken up and retained by aquatic and terrestrial plants and is concentrated in the liver and kidney of animals that eat the plants (Elinder 1985a).

For the U.S. population, cadmium exposure through the drinking water supply is of minor concern. EPA requires water suppliers to limit the cadmium concentration in water to <5 µg/L (EPA 2006a).

In the United States, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake (NTP 2005). Based on the mean cadmium daily intakes of males and females aged 6–60 years reported by Choudhury et al. (2001), age-weighted mean cadmium intakes of 0.35 µg/kg/day for males and 0.30 µg/kg/day for females were calculated for U.S. nonsmokers. In general, vegetables, particularly leafy vegetables such as lettuce (0.051 mg/kg) and spinach (0.124 mg/kg), have the highest concentrations of cadmium; the concentrations of cadmium in all vegetables ranged from 0.001 to 0.124 mg/kg (FDA 2010; Morrow 2001). Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium (Morrow 2001); the mean concentration of cadmium in legumes and nuts ranged from 0.001 to 0.054 mg/kg (FDA 2010). People who regularly consume shellfish and organ meats (liver and

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kidney) have an increased risk of cadmium exposure, as these organisms tend to accumulate cadmium (Elinder 1985a).

Tobacco leaves naturally accumulate cadmium (Morrow 2001). Cadmium levels in cigarettes vary greatly depending on the source of production. Cigarettes produced in Mexico were found to have the highest level of cadmium per cigarette (arithmetic mean [AM] \pm arithmetic standard deviation [ASD] = $2.03 \mu\text{g}/\text{cigarette} \pm 0.33$), while cigarettes from India were found to have the lowest (arithmetic mean \pm arithmetic standard deviation = $0.35 \mu\text{g}/\text{cigarette} \pm 0.09$). The arithmetic mean for the United States was $1.07 \mu\text{g}/\text{cigarette} \pm 0.11$ (Watanabe et al. 1987). Tobacco contains approximately $0.5\text{--}2.0 \mu\text{g}$ cadmium per cigarette, and about 10% is inhaled when smoked (Morrow 2010). The geometric mean blood cadmium level for the heavy smoker subgroup in New York City was reported as $1.58 \mu\text{g}/\text{L}$, compared to the geometric mean of $0.77 \mu\text{g}/\text{L}$ for all New York City adults (McKelvey et al. 2007).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

Additional releases of cadmium to the environment occur from natural sources and from processes such as combustion of fossil fuel, incineration of municipal or industrial wastes, or land application of sewage sludge or fertilizer (EPA 1985a). Quantitative information on releases of cadmium to specific environmental media is discussed below.

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6.2.1 Air

Estimated releases of 731 pounds (~0.3 metric tons) of cadmium to the atmosphere from 41 domestic manufacturing and processing facilities in 2009, accounted for about 0.18% of the estimated total environmental releases of cadmium from facilities required to report to the TRI (TRI09 2011). These releases are summarized in [Table 6-1](#). Estimated releases of 11,567 pounds (~5.2 metric tons) of cadmium compounds to the atmosphere from 85 domestic manufacturing and processing facilities in 2009, accounted for about 0.55% of the estimated total environmental releases of cadmium from facilities required to report to the TRI (TRI09 2011). These releases are summarized in [Table 6-2](#).

Cadmium is released to the atmosphere from both natural and anthropogenic sources. Cadmium is widely distributed in the earth's crust (EPA 1985a) with concentrations reported between 0.1 and 0.5 ppm and higher levels in sedimentary rocks (Morrow 2001). Consequently, cadmium may be released to the air from entrainment of dust particles, volcanic eruptions, forest fires, or other natural phenomena (EPA 1985a; Morrow 2001). Cadmium exists in ocean waters at average levels ranging from <5 to 110 ng/L and may transport to the atmosphere through natural processes like generation of sea-salt aerosols (Morrow 2001; Shevchenko et al. 2003). Increased cadmium levels in the air over the Russian Arctic have been detected during the summer and autumn seasons and are believed to be attributed to natural processes, while the levels detected during the winter and spring seasons were due to anthropogenic sources (Shevchenko et al. 2003).

However, industrial activities are the main sources of cadmium release to air (EPA 1985a), and emissions from anthropogenic sources have been found to exceed those of natural origin by an order of magnitude (IARC 1993). Major industrial sources of cadmium emissions include zinc, lead, copper, and cadmium smelting operations; coal and oil-fired boiler; other urban and industrial emissions; phosphate fertilizer manufacture; road dust; and municipal and sewage sludge incinerators (Alloway and Steinnes 1999; Morrow 2001). Emission of cadmium through nonferrous metal production in 1995 was highest in Asia with 1,176 tonnes and North America emitting 191 tonnes. Estimated emissions of cadmium from municipal waste and sewage sludge incineration in North America were 8 and 7 tonnes/year, respectively, in the mid-1990s (Pacyna and Pacyna 2001). Additional sources that contribute negligible amounts of cadmium are rubber tire wear, motor oil combustion, cement manufacturing, and fertilizer and fungicide application (Wilber et al. 1992). Average cadmium emission factors for combustion of coal and oil are about 0.1 and 0.05 g/ton, respectively. Cement production releases an estimated 0.01 g/ton cement and

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Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium^a

Reported amounts released in pounds per year ^b									
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ^j	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AL	2	13	122	0	36,955	11	37,087	13	37,100
AR	3	4	7	0	0	100	6	105	111
AZ	1	0	0	0	16,005	0	16,005	0	16,005
CA	2	426	169	0	13,992	20	14,263	344	14,607
FL	1	0	0	0	0	0	0	0	0
GA	1	26	0	0	5	0	26	5	31
IA	1	0	0	0	0	0	0	0	0
IN	1	3	0	0	0	0	3	0	3
KS	2	0	0	0	0	0	0	0	0
KY	1	19	0	0	0	0	19	0	19
LA	2	75	0	0	61	0	136	0	136
MI	1	0	0	0	5	0	0	5	5
NC	2	30	0	0	0	0	30	0	30
NE	1	1	0	0	10,282	0	10,249	34	10,283
NV	1	2	0	0	40,681	524	40,683	524	41,207
NY	2	0	11	0	0	8	11	8	19
OH	4	7	0	104,579	22,337	1	126,586	338	126,924
OK	1	13	0	0	38,780	0	38,793	0	38,793
OR	1	1	0	0	13,575	1	13,577	1	13,577
PA	1	59	3	0	0	0	62	0	62
TN	2	5	0	0	38,186	2,519	5	40,705	40,710
TX	3	1	22	37,988	0	26	37,990	47	38,037
UT	3	11	4	0	22,020	2,849	22,031	2,853	24,884
VA	1	0	0	0	0	0	0	0	0

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Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium^a

Reported amounts released in pounds per year ^b									
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
WI	1	35	0	0	181	0	35	181	216
Total	41	731	338	142,567	253,065	6,059	357,597	45,164	402,760

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI09 2011 (Data are from 2009)

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Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium Compounds^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AK	3	129	3	0	61,176	0	61,308	0	61,308
AL	4	221	122	0	698,581	0	698,681	243	698,924
AR	1	0	0	0	0	131	0	131	131
AZ	3	611	5	0	63,392	0	63,753	255	64,008
CA	1	0	0	0	115	0	0	115	115
CO	1	1	0	0	0	0	1	0	1
CT	1	0	0	0	0	0	0	0	0
FL	1	0	0	0	0	0	0	0	0
GA	3	8	3	0	0	0	9	3	11
ID	2	6,409	6	0	386,455	0	392,870	0	392,870
IL	5	59	117	215	33,651	1,553	1,289	34,306	35,595
IN	3	76	6	0	13,361	41	82	13,402	13,484
LA	1	0	0	0	0	0	0	0	0
MA	3	25	251	0	0	1,021	25	1,272	1,297
MD	1	0	0	0	0	12,400	0	12,400	12,400
MI	1	0	5	0	250	0	0	255	255
MO	1	593	265	0	6,178	9	6,987	58	7,045
NC	1	0	0	0	0	0	0	0	0
NE	1	250	0	0	250	21,000	250	21,250	21,500
NJ	2	5	1	0	1,488	140	5	1,629	1,634
NV	4	40	0	0	165,471	0	165,506	5	165,511
NY	1	0	21	0	0	0	21	0	21
OH	10	37	102	0	4,264	15,604	1,471	18,536	20,007
OK	1	31	0	0	0	0	31	0	31
PA	8	646	326	0	2,596	9,442	721	12,289	13,010
SC	1	255	10	0	6,165	0	265	6,165	6,430
TN	5	1,997	597	0	192,927	428	195,516	433	195,949
TX	7	30	335	2,118	334,113	2,583	334,650	4,529	339,179
UT	4	130	133	0	54,954	107	55,217	107	55,324
WA	1	2	2	0	0	5	4	5	9
WI	3	10	27	0	1	6,623	10	6,651	6,661

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Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Cadmium Compounds^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							Total release	
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	On-site ^j	Off-site ^k	On- and off-site	
WV	1	2	7	0	1,018	0	518	509	1,027	
Total	85	11,567	2,346	2,333	2,026,406	71,087	1,979,190	134,549	2,113,739	

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI09 2011 (Data are from 2009)

6. POTENTIAL FOR HUMAN EXPOSURE

pig iron and steel production releases an estimated 0.1 g/ton (Pacyna and Pacyna 2001). Atmospheric cadmium exists mainly in the forms of cadmium oxide and cadmium chloride (Morrow 2001).

Cadmium emissions have decreased dramatically since the 1960s as primary cadmium producers now use the electrolytic process and pollution control technologies such as agglomeration, electrostatic purification of gas exhaust, and exhaust filtration have been implemented (Herron 2003; Morrow 2001; Schulte-Schrepping and Piscator 2002). Anthropogenic cadmium emissions have decreased by over 90% in the last 50 years (Morrow 2010).

There is a potential for release of cadmium to air from hazardous waste sites. Cadmium has been detected in air samples collected at 50 of the 1,014 NPL hazardous waste sites where cadmium was detected in some environmental medium (HazDat 2007). Cadmium compounds were detected in air samples collected at one of three NPL hazardous waste sites where cadmium compounds were detected. The HazDat information used includes data from NPL sites only.

6.2.2 Water

Estimated releases of 338 pounds (~0.15 metric tons) of cadmium to surface water from 41 domestic manufacturing and processing facilities in 2009, accounted for about 0.084% of the estimated total environmental releases from facilities required to report to the TRI. This estimate includes releases to wastewater treatment and publicly owned treatment works (TRI09 2011). These releases are summarized in [Table 6-1](#). Estimated releases of 2,346 pounds (~1.1 metric tons) of cadmium compounds to surface water from 85 domestic manufacturing and processing facilities in 2009, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI. This estimate includes releases to wastewater treatment and publicly owned treatment works (TRI09 2011). These releases are summarized in [Table 6-2](#).

Cadmium may be released to water by natural weathering processes, by discharge from industrial facilities or sewage treatment plants, atmospheric deposition, by leaching from landfills or soil, or phosphate fertilizers (EPA 1981a, 1985a; IJC 1989; Morrow 2001). Cadmium may also leach into drinking water supplies from pipes in the distribution system (Elinder 1985a). The average level of cadmium in ocean water has been reported between <5 and 110 ng/L, with higher levels reported near coastal areas and in marine phosphates and phosphorites (Morrow 2001).

6. POTENTIAL FOR HUMAN EXPOSURE

Smelting of nonferrous metal ores has been estimated to be the largest anthropogenic source of cadmium released into the aquatic environment. Cadmium contamination can result from entry into aquifers of mine drainage water, waste water, tailing pond overflow, and rainwater runoff from mine areas (IARC 1993). The upper Clark Fork River in Montana is contaminated with large amounts of cadmium from past mining activities between 1880 and 1972. While mining wastes are no longer released into the river, an estimated 14.5 million cubic meters of tailings have been incorporated into the river bed, floodplain, and reservoir sediments (Canfield et al. 1994). Other human sources include spent solutions from plating operations and phosphate fertilizers. Cadmium constitutes up to 35 mg/kg of phosphorous pentoxide, a component of phosphate-based fertilizers, in the United States (IARC 1993). Atmospheric fallout of cadmium to aquatic systems is another major source of cadmium to the environment (IARC 1993; Muntau and Baudo 1992).

A large proportion of the cadmium load in the aquatic environment is due to diffuse pollution originating from many different sources rather than from point sources. In the estuarine portion of the Hudson River, it has been found that more cadmium was released from agricultural and urban run-off than from industrial and municipal sewage treatment plants (Muntau and Baudo 1992). In an urban environment, there are also multiple sources of cadmium to waste water. In an urban waste water study conducted in the United Kingdom, cadmium was detected in the waste water originating from industrial, commercial, and private sectors, with the highest average cadmium concentration detected in the waste water of new (<5 years old) private housing (0.375 µg/L) (Rule et al. 2006).

There is also a potential for release of cadmium to water from hazardous waste sites. Cadmium has been detected in surface water samples collected at 354 of the 1,014 NPL hazardous waste sites, and in groundwater samples collected at 675 of the 1,014 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 2007). The HazDat information used includes data from NPL sites only.

6.2.3 Soil

Estimated releases of 253,065 pounds (~115 metric tons) of cadmium to soils from 41 domestic manufacturing and processing facilities in 2009, accounted for about 63% of the estimated total environmental releases of cadmium from facilities required to report to the TRI (TRI09 2011). An additional 142,567 pounds (~65 metric tons), constituting about 35% of the total environmental emissions, were released via underground injection and to Class I wells, Class II-V wells (TRI09 2011).

6. POTENTIAL FOR HUMAN EXPOSURE

These releases are summarized in Table 6-1. Estimated releases of 2,026,406 pounds (~919 metric tons) of cadmium compounds to soils from 85 domestic manufacturing and processing facilities in 2009, accounted for about 96% of the estimated total environmental releases from facilities required to report to the TRI. An additional 2,333 pounds (~1 metric tons), constituting about 0.1% of the total environmental emissions, were released via underground injection and to Class I wells, Class II-V wells (TRI09 2011). These releases are summarized in Table 6-2.

Major sources of cadmium to soil include atmospheric emissions, direct application, and accidental or fugitive contamination. Direct application emissions refer to phosphate fertilizers, phosphogypsum and other byproduct gypsums (from the manufacture of phosphoric acid and phosphorite), sewage sludges, composted municipal solid waste, and residual ashes from wood, coal, or other types of combustion. Contamination sources include industrial site contamination, mine waste dumps, and corrosion of metal structures (Alloway and Steinnes 1999).

Approximately 61% of the 5.6 million dry tons of sewage sludge produced annually in the United States is landspread (NRC 2002). The EPA ceiling limit for the cadmium content of sludge applied to land is 85 mg/kg in sewage sludge, the cumulative pollution loading rate is 39 kg/ha, and the maximum annual cadmium loading of $1.9 \text{ kg-ha}^{-1}\cdot\text{year}^{-1}$ (EPA 2011a). Estimated cadmium concentrations in sewage sludge range from 0.21 to $>11.8 \text{ mg/kg}$ (EPA 2009a). Sludges from treatment plants that serve cadmium industries (i.e., battery manufacturing) tend to have higher levels of cadmium (Alloway and Steinnes 1999).

Phosphate fertilizers are a major source of cadmium input to agricultural soils (EPA 1985a). The natural cadmium concentration in phosphates ranges from 3 to $100 \text{ }\mu\text{g/g}$ (EPA 1985a; Singh 1994). Some may contain up to 300 mg Cd/kg (Alloway and Steinnes 1999). It is estimated that over 8 million tons of phosphate fertilizer were used in the United States in 2010 (USDA 2012). Any soil treated with these fertilizers will have a cadmium input, but exactly how much will vary (Alloway and Steinnes 1999). For example, continuous fertilization with a high rate of triple super-phosphate ($1,175 \text{ kg P-ha}^{-1}\cdot\text{year}^{-1}$) for a period of 36 years resulted in a 14-fold increase in cadmium content of surface soils (Singh 1994).

Wet and dry deposition of cadmium from the atmosphere may also contribute sizable amounts of cadmium to soil in the areas surrounding sources of atmospheric emissions, such as incinerators and vehicular traffic, which may release cadmium from burned fuel and tire wear (EPA 1985a; Mielke et al. 1991). High-temperature sources, such as smelters and incinerators, release small particles that are ideal

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for long-range atmospheric transport. Also, vapors emitted from high temperature processes will preferentially condense onto smaller particles, thus making vapor emissions available for transport (Steinnes and Friedland 2006). Aerosols containing cadmium can be carried very long distances in the atmosphere before being deposited to soils. In the soils in southern Norway, most of the cadmium and other heavy metals that are deposited from the atmosphere originate from other parts of Europe (Alloway and Steinnes 1999). Long-range atmospheric deposition is more evident in organic-rich soils as they have a tendency to concentrate heavy metals (Steinnes and Friedland 2006).

There is also a potential for release of cadmium to soil from hazardous waste sites. Cadmium has been detected in soil samples collected at 606 of the 1,014 NPL hazardous waste sites and in sediment samples collected at 392 of the 1,014 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 2007). The HazDat information used includes data from NPL sites only.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Cadmium is expected to partition primarily to soil (80–90%) when released to the environment.

Although particulate and vapor cadmium may be released to the air, the net flux to soil will be positive as cadmium will eventually deposit onto soils (Morrow 2001; Wilber et al. 1992).

Cadmium and cadmium compounds have negligible vapor pressures (see [Table 4-2](#)) but can be released to the environment by emissions from municipal waste incinerators, nonferrous metal production, and other high-temperature processes (Morrow 2001). Cadmium emitted to the atmosphere from combustion processes condense onto very small particulates that are in the respirable range ($<10\ \mu\text{m}$) and are subject to long-range transport (Steinnes and Friedland 2006; Wilber et al. 1992). These cadmium pollutants may be transported from a hundred to a few thousand kilometers and have a typical atmospheric residence time of about 1–10 days before deposition occurs (EPA 1980d). Larger cadmium-containing particles from smelters and other pollutant sources are also removed from the atmosphere by gravitational settling, with substantial deposition in areas downwind of the pollutant source. Cadmium-containing particulates may dissolve in atmospheric water droplets and be removed from air by wet deposition.

Cadmium is more mobile in aquatic environments than most other heavy metals (e.g., lead). In most natural surface waters, the affinities of complexing ligands for cadmium generally follow the order of humic acids $> \text{CO}_3^{2-} > \text{OH}^- \geq \text{Cl}^- \geq \text{SO}_4^{2-}$ (EPA 1979). In unpolluted natural waters, most cadmium

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transported in the water column will exist in the dissolved state as the hydrated ion $\text{Cd}(\text{H}_2\text{O})_6^{2+}$. Minor amounts of cadmium are transported with the coarse particulates, and only a small fraction is transported with the colloids. In unpolluted waters, cadmium can be removed from solution by exchange of cadmium for calcium in the lattice structure of carbonate minerals (EPA 1979). In polluted or organic-rich waters, adsorption of cadmium by humic substances and other organic complexing agents plays a dominant role in transport, partitioning, and remobilization of cadmium (EPA 1979). Cadmium concentration in water is inversely related to the pH and the concentration of organic material in the water (EPA 1979). Because cadmium exists only in the +2 oxidation state in water, aqueous cadmium is not strongly influenced by the oxidizing or reducing potential of the water. However, under reducing conditions, cadmium may form cadmium sulfide, which is poorly soluble and tends to precipitate (EPA 1983c; McComish and Ong 1988). Free (ionic) cadmium seems to be the toxic form and becomes much more prevalent at low salinity (Sprague 1986). Cadmium has a relatively long residence time in aquatic systems. In Lake Michigan, a mean residence time of 4–10 years was calculated for cadmium compared to 22 years calculated for mercury (Wester et al. 1992).

Precipitation and sorption to mineral surfaces, hydrous metal oxides, and organic materials are the most important processes for removal of cadmium to bed sediments. Humic acid is the major component of sediment responsible for adsorption. Sorption increases as the pH increases (EPA 1979). Sediment bacteria may also assist in the partitioning of cadmium from water to sediments (Burke and Pfister 1988). Both cadmium-sensitive and cadmium-resistant bacteria reduced the cadmium concentration in the water column from 1 ppm to between 0.2 and 0.6 ppm, with a corresponding increase in cadmium concentration in the sediments in the simulated environment (Burke and Pfister 1988). Studies indicate that concentrations of cadmium in sediments are at least one order of magnitude higher than in the overlying water (EPA 1979). The mode of sorption of cadmium to sediments is important in determining its disposition to remobilize. Cadmium associated with carbonate minerals, precipitated as stable solid compounds or co-precipitated with hydrous iron oxides, is less likely to be mobilized by resuspension of sediments or biological activity. Cadmium that is adsorbed to mineral surfaces such as clay, or to organic materials, is more easily bioaccumulated or released in the dissolved state when the sediment is disturbed (EPA 1979). Cadmium may redissolve from sediments under varying ambient conditions of pH, salinity, and redox potential (DOI 1985; EPA 1979; Feijtel et al. 1988; Muntau and Baudo 1992). Cadmium is not known to form volatile compounds in the aquatic environment, so partitioning from water to the atmosphere does not occur (EPA 1979).

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Debusk et al. (1996) studied the retention and compartmentalization of lead and cadmium in wetland microcosms. Differences between measured concentrations in inflow and outflow samples indicated that approximately half of the added cadmium was retained in the wetland microcosms. Experiments showed that nearly all trace metals were present in the sediments as sulfides, limiting their bioavailability and toxicity. The results of their analyses and a lack of noticeable biological effects suggested that in wetlands containing organic sediments, the sediment chemistry dominates cycling of the trace metals.

In soils, pH, oxidation-reduction reactions, and formation of complexes are important factors affecting the mobility of cadmium (Bermond and Bourgeois 1992; Herrero and Martin 1993). Cadmium can participate in exchange reactions on the negatively charged surface of clay minerals. In acid soils, the reaction is reversible. However, adsorption increases with pH and may become irreversible (Herrero and Martin 1993). Cadmium also may precipitate as insoluble cadmium compounds, or form complexes or chelates by interaction with organic matter. Available data suggest that organic matter is more effective than inorganic constituents in keeping cadmium unavailable (McBride 1995). Examples of cadmium compounds found in soil are $\text{Cd}_3(\text{PO}_4)_2$, CdCO_3 , and $\text{Cd}(\text{OH})_2$ (Herrero and Martin 1993). These compounds are formed as the pH rises. It has been found that about 90% of cadmium in soils remains in the top 15 cm (Anonymous 1994).

The mobility and plant availability of cadmium in wetland soils are substantially different from upland soils. Cadmium tends to be retained more strongly in wetland soils and is more available to plants under upland conditions (Gambrell 1994). Debusk et al. (1996) compared heavy metal uptake by cattails and duckweed wetland microcosms and found that duckweed, on a whole-plant basis, accumulates cadmium more effectively than cattail does. The potential cadmium removal rate for duckweed is 2–4 mg $\text{Cd}/\text{m}^2/\text{day}$.

Cadmium in soils may leach into water, especially under acidic conditions (Elinder 1985a; EPA 1979). Roy et al. (1993) demonstrated that chlorine complexation in the leachate of ash from a municipal solid waste incinerator can result in a decrease in cadmium sorption by two common clays, kaolinite and illite. They also found that cationic competitive sorption enhances mobility in soils. Cadmium-containing soil particles may also be entrained into the air or eroded into water, resulting in dispersion of cadmium into these media (EPA 1985a). Contamination of soil by cadmium is of concern because the cadmium is taken up efficiently by plants and, therefore, enters the food chain for humans and other animals. A low soil pH, which is becoming prevalent in many areas of the world due to acid rain, increases the uptake of cadmium by plants (Elinder 1992).

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Aquatic and terrestrial organisms bioaccumulate cadmium (Handy 1992a, 1992b; Kuroshima 1992; Naqvi and Howell 1993; Roseman et al. 1994; Suresh et al. 1993). Cadmium concentrates in freshwater and marine animals to concentrations hundreds to thousands of times higher than in the water (EPA 1979). Reported bioconcentration factors (BCFs) range from <200 to 18,000 for invertebrates (van Hattum et al. 1989), from 3 to 4,190 for fresh water aquatic organisms (ASTER 1995), and from 5 to 3,160 for saltwater aquatic organisms (ASTER 1994). Bioconcentration in fish depends on the pH and the humus content of the water (John et al. 1987). Because of their high ability to accumulate metals, some aquatic plants have been suggested for use in pollution control. For example, it has been suggested that the rapidly-growing water hyacinth (*Eichhornia crassipes*) could be used to remove cadmium from domestic and industrial effluents (Ding et al. 1994; Muntau and Baudo 1992).

The data indicate that cadmium bioaccumulates in all levels of the food chain. Cadmium accumulation has been reported in grasses and food crops, and in earthworms, poultry, cattle, horses, and wildlife (Alloway et al. 1990; Beyer et al. 1987; Gochfeld and Burger 1982; Kalac et al. 1996; Munshower 1977; Ornes and Sajwan 1993; Rutzke et al. 1993; Sileo and Beyer 1985; Vos et al. 1990). The metal burden of a crop depends on uptake by the root system, direct foliar uptake and translocation within the plant, and surface deposition of particulate matter (Nwosu et al. 1995). In general, cadmium accumulates in the leaves of plants and, therefore, is more of a risk in leafy vegetables grown in contaminated soil than in seed or root crops (Alloway et al. 1990). He and Singh (1994) report that, for plants grown in the same soil, accumulation of cadmium decreased in this order: leafy vegetables, root vegetables, and grain crops. Alloway et al. (1990) also demonstrated that uptake of cadmium decreased in this order: lettuces, cabbages, radishes, and carrots. Nwosu et al. (1995) investigated the uptake of cadmium and lead in lettuce and radish grown in loam soil spiked with known mixtures of CdCl_2 and $\text{Pb}(\text{NO}_3)_2$. They found that the mean uptake of cadmium by lettuce and radish increased as the concentrations of cadmium and lead in the soil increased. Their results supported previous findings that cadmium is absorbed by passive diffusion and translocated freely in the soil. The observed decline in cadmium uptake by lettuce at 400 mg/kg could be attributed to saturation of the active binding sites on the plant root system or by early toxicological responses of the plant root. The study also supported earlier findings that radish did not accumulate as much cadmium as lettuce.

Some studies have concluded that soil pH is the major factor influencing plant uptake of cadmium from soils (Smith 1994). Amending soil with lime raises the pH, increasing cadmium adsorption to the soil and reducing bioavailability (He and Singh 1994; Thornton 1992). One study found that in peeled potato

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tubers, potato peelings, oat straw, and ryegrass, cadmium concentrations generally decreased as simple linear functions of increasing soil pH over the range of pH values measured (pH 3.9–7.6) (Smith 1994). Soil type also affects uptake of cadmium by plants. For soils with the same total cadmium content, cadmium has been found to be more soluble and more plant-available in sandy soil than in clay soil (He and Singh 1994). Similarly, cadmium mobility and bioavailability are higher in noncalcareous than in calcareous soils (Thornton 1992). Oxidation-reduction potential may also have a large effect on soil-to-plant cadmium transport. The absorption of cadmium paddy rice is significantly affected by the oxidation-reduction potential of the soil. The oxidation-reduction potential of rice paddy soils shifts drastically compared to upland soils due to submerging and draining techniques. Cadmium to rice ratios (cadmium concentration in brown rice/cadmium concentration in soil) were the smallest when the rice was grown under submerged conditions during the whole growth period. The ratios were the largest when the soil (coarse Toyama soil) was drained after the tillering stage. This is due to changes in cadmium solubility. Under flooded conditions, cadmium sulfide formation increases, and thus, cadmium solubility decreases (Iimura 1981).

Since cadmium accumulates largely in the liver and kidneys of vertebrates and not in the muscle tissue (Harrison and Klaverkamp 1990; Sileo and Beyer 1985; Vos et al. 1990), and intestinal absorption of cadmium is low, biomagnification through the food chain may not be significant (Sprague 1986). In a study of marine organisms from the Tyrrhenian Sea, no evidence of cadmium biomagnification was found along pelagic or benthic food webs (Bargagli 1993). Although some data indicate increased cadmium concentrations in animals at the top of the food chain, comparisons among animals at different trophic levels are difficult, and the data available on biomagnification are not conclusive (Beyer 1986; Gochfeld and Burger 1982). Nevertheless, uptake of cadmium from soil by feed crops may result in high levels of cadmium in beef and poultry (especially in the liver and kidneys). This accumulation of cadmium in the food chain has important implications for human exposure to cadmium, whether or not significant biomagnification occurs.

Boularbah et al. (1992) isolated six cadmium-resistant bacterial strains from a soil receiving dredged sediments and containing 50 mg Cd/kg. The isolates tolerated higher cadmium concentrations than the control strain and accumulated cadmium at concentrations ranging from 0 to 100 mg/L. One of the isolates, *Bacillus brevis*, was found to be the most resistant to cadmium, with the ability to accumulate up to 70 mg Cd/g of cells dry weight, and may have some use in reclamation of metal-contaminated soils.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Little information is available on the atmospheric reaction of cadmium (EPA 1980d). The common cadmium compounds found in air (oxide, sulfate, chloride) are stable and not subject to photochemical reactions (EPA 1980d). Cadmium sulfide may photolyze to cadmium sulfate in aqueous aerosols (Konig et al. 1992). Transformation of cadmium among types of compounds in the atmosphere is mainly by dissolution in water or dilute acids (EPA 1980d).

6.3.2.2 Water

In fresh water, cadmium is present primarily as the cadmium(+2) ion and $\text{Cd}(\text{OH})_2$ and CdCO_3 complexes, although at high concentrations of organic material, more than half may occur in organic complexes (McComish and Ong 1988). Some cadmium compounds, such as cadmium sulfide, cadmium carbonate, and cadmium oxide, are practically insoluble in water. However, water-insoluble compounds can be changed to water-soluble salts by interaction with acids or light and oxygen. For example, aqueous suspensions of cadmium sulfide can gradually photooxidize to soluble cadmium (IARC 1993). Cadmium complexation with chloride ion increases with salinity until, in normal seawater, cadmium exists almost entirely as chloride species (CdCl^+ , CdCl_2 , CdCl_3^-) with a minor portion as Cd^{2+} . In reducing environments, cadmium precipitates as cadmium sulfide in the presence of sulfide ions (McComish and Ong 1988). Photolysis is not an important mechanism in the aquatic fate of cadmium compounds (EPA 1983c), nor is biological methylation likely to occur (EPA 1979).

6.3.2.3 Sediment and Soil

Transformation processes for cadmium in soil are mediated by sorption from and desorption to water, and include precipitation, dissolution, complexation, and ion exchange (McComish and Ong 1988). Important factors affecting transformation in soil include the cation exchange capacity, pH, and content of clay minerals, carbonate minerals, oxides, organic matter, and oxygen (McComish and Ong 1988).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to cadmium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of cadmium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits

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of current analytical methods. In reviewing data on cadmium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring cadmium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Cadmium levels in ambient air generally range from 0.1 to 5 ng/m³ in rural areas, 2–15 ng/m³ in urban areas, and 15–150 ng/m³ in industrialized areas. Remote areas can contain lower levels of cadmium (Morrow 2001). Cadmium can undergo long-range atmospheric transport and deposition causing cadmium contamination in areas with no local cadmium inputs. Smoking can greatly affect indoor air concentrations of cadmium. In nonsmoking environments, there is little difference between indoor and outdoor air quality (Morrow 2001). Monitoring studies conducted for EPA's 2006 Final Report for the Urban Air Toxics Monitoring Program detected cadmium in ambient air at several monitoring sites throughout the United States. At all detection sites in Bountiful, Utah; Northbrook, Illinois; Austin, Texas; St. Louis, Missouri; Indianapolis, Indiana; and Birmingham, Alabama average daily cadmium levels in ambient air were <0.01 µg/m³. In Bountiful, Utah average daily cadmium levels were reported as 0.0008 µg/m³ (EPA 2007).

Emission rates of cadmium from solid waste incinerators have been found to range from 20 to 2,000 µg/m³ from the stacks of traditional incinerators and from 10 to 40 µg/m³ from advanced incinerators. Advances in pollution control and increased government regulations have resulted in decreased cadmium emissions to the environment (EPA 1990a; Herron 2003; Morrow 2001; Schulte-Schrepping and Piscator 2002). Although there may be an increase in fossil fuel combustion and waste incineration, it does not appear likely that overall cadmium emissions to air will increase substantially in the United States.

Cadmium levels in aerosols over Russian Arctic seas were measured in order to understand the magnitude of long-range atmospheric deposition. Ten-year average monthly mean concentrations ranged from 0.002 to 0.080 ng/m³ in Franz Josef Land and from 0.0026 to 0.048 ng/m³ in Sevemaya Zemlya. The highest concentrations were reported in the spring season and the lowest concentrations reported in the autumn for both sampling sites. During the winter and spring months, it was estimated that >50% of the average air pollutant concentrations in the Russian Arctic are due to atmospheric pollution. The

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anthropogenic sources of cadmium to the Russian Arctic are the industrial areas of Northern Europe, Kola Peninsula, and the Urals and Norilsk regions (Shevchenko et al. 2003).

Atmospheric concentrations of cadmium are generally highest in the vicinity of cadmium-emitting industries such as smelters, municipal incinerators, or fossil fuel combustion facilities (Elinder 1985a; Pirrone et al. 1996). The mean annual concentration of airborne cadmium in an area about 1 km from a zinc smelter in Colorado was $0.023 \mu\text{g}/\text{m}^3$ ($2.3 \times 10^{-5} \text{ mg}/\text{m}^3$) (IARC 1993). Sweet et al. (1993) conducted a study of airborne inhalable particulate matter (PM-10) over a 2-year period in two urban/industrial areas (southeast Chicago and East St. Louis) and one rural area in Illinois. There was a significant difference between the cadmium levels in the urban areas and the cadmium levels in the rural area. Cadmium concentrations in the East St. Louis area were 5–10 times higher, with a range of <4 to $115 \text{ ng}/\text{m}^3$ (average $15[24] \text{ ng}/\text{m}^3$) for fine particles and a range of <4–97 ng/m^3 (average $10[18] \text{ ng}/\text{m}^3$) for coarse particles. In the Kikinda region of Serbia and Montenegro, where metal processing and construction industries are located, a mean annual atmospheric deposit of $36.0 \mu\text{g}/\text{m}^2$ per day was reported in 1995. A period of decreased industrial production, which decreased atmospheric cadmium deposits by 93%, resulted in 17% cadmium reduction in cattle feed and 13% in milk (Vidovic et al. 2005). Moss studies conducted by Hasselbach et al. (2005) in the area of the Red Dog Mine in Alaska reported cadmium levels $>24 \text{ mg}/\text{kg}$ dry weight in moss adjacent to the ore haul road. Ore dust containing heavy metals escapes from the ore trucks on the haul road and can be deposited in the nearby area (Hasselbach et al. 2005).

Annual average concentrations of atmospheric cadmium over three Great Lakes reflect the influence of industrialization and urbanization; Lake Erie's levels of $0.6 \text{ ng}/\text{m}^3$ were higher than fine particle concentrations of $0.2 \text{ ng}/\text{m}^3$ over Lake Michigan and $<0.2 \text{ ng}/\text{m}^3$ over Lake Superior (Sweet et al. 1998). In the Lake Michigan Urban Air Toxics Study of dry deposition of metals, the flux of cadmium on the south side of Chicago was reported at about $0.01 \text{ mg}/\text{m}^2/\text{day}$ and levels in rural Michigan and over Lake Michigan were far lower (Holsen et al. 1993).

6.4.2 Water

The average level of cadmium in ocean water has been reported between <5 and $110 \text{ ng}/\text{L}$, with higher levels reported near coastal areas and in marine phosphates and phosphorites (Morrow 2001).

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Thornton (1992) reports that waters from the vicinity of cadmium-bearing mineral deposits may have cadmium concentrations of $\geq 1,000$ $\mu\text{g/L}$. The cadmium concentration of natural surface water and groundwater is usually < 1 $\mu\text{g/L}$ (Elinder 1985a, 1992). EPA requires water suppliers to limit the cadmium concentration in drinking water to < 5 $\mu\text{g/L}$ (EPA 2006a).

Groundwater in New Jersey has an estimated median level of 1 $\mu\text{g Cd/L}$ with a high level of 405 $\mu\text{g/L}$. In a survey of groundwater surrounding waste sites, a concentration of 6,000 $\mu\text{g Cd/L}$ was found (NTP 1994). The National Urban Runoff Program measured cadmium concentrations in urban storm water runoff; concentrations ranged from 0.1 to 14 $\mu\text{g/L}$ in 55% of samples that were positive for cadmium (Cole et al. 1984). Cadmium in highway run-off has been detected at levels of 0.0–0.06 mg/L (0.0–60 $\mu\text{g/L}$).

In the estuarine portion of the Hudson River, more cadmium was released from agricultural and urban run-off than from industrial and municipal sewage treatment plants (Muntau and Baudo 1992). In an urban environment, there are also multiple sources of cadmium to waste water, based on an urban waste water study conducted in the United Kingdom. Cadmium was detected in the waste water originating from industrial, commercial, and private sectors, with the highest average cadmium concentration detected in the foul water of new (< 5 years old) private housing (0.375 $\mu\text{g/L}$) (Rule et al. 2006). Cadmium was detected in the contaminated groundwater plume near in the Moon Creek watershed in the Couer D'Alene Mining District of Idaho at concentrations of ≤ 0.077 mg/L . The cadmium was transported to the creek with the plume where it was subsequently diluted (Paulson 1997). In the Spring River Basin of Kansas, Missouri, and Oklahoma, part of the Tri-State Mining District, cadmium was detected in surface waters at concentrations ranging from < 1.0 to 24 $\mu\text{g/L}$ (peak flow) and from < 1.0 to 75.0 $\mu\text{g/L}$ (base flow). It was detected in the sediment of the sampling sites at concentrations ranging from 0.62 to 300 $\mu\text{g/g}$ dry weight in the < 250 μm sediment fraction and from 0.89 to 180 $\mu\text{g/g}$ dry weight in the < 63 μm fraction (Angelo et al. 2007).

6.4.3 Sediment and Soil

Cadmium concentrations in soils not contaminated by anthropogenic sources range from 0.06 to 1.1 mg/kg , with a minimum of 0.01 mg/kg and a maximum of 2.7 mg/kg (Alloway and Steinnes 1999). Cadmium content in marine sediments ranges from 0.1 to 1.0 $\mu\text{g/g}$ (ppm) in the Atlantic and Pacific oceans (Thornton 1992). Average cadmium concentration in agricultural soils of remote locations was reported as 0.27 mg/kg (Holmgren et al. 1993). Soils with parent materials such as black shale (cadmium

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content up to 24 mg/kg) may have higher concentrations of natural cadmium. Since the U.S. mandatory limit of cadmium in sewage sludge is <20 mg/kg, soils receiving sewage sludge should not have heightened cadmium levels (Alloway and Steinnes 1999). Topsoil concentrations are often more than twice as high as subsoil levels as the result of atmospheric fallout and contamination (Pierce et al. 1982). Cadmium will partition mostly to soil and sediment when released to the environment. Atmospheric deposition is a major source of surface soil contamination, which allows cadmium to be introduced into the food supply (Alloway and Steinnes 1999; Morrow 2001).

Markedly elevated levels may occur in topsoils near sources of contamination. Moss studies conducted by Hasselbach et al. (2005) in the area of the Red Dog Mine in Alaska reported cadmium levels >24 mg/kg dry weight in moss (n=151), as a measure atmospheric deposition onto soil surfaces, within 10 m of the ore haul road. Ore dust containing heavy metals escapes from the ore trucks during loading and unloading at the mine and port site settles on the surfaces of the trucks, which blow off the trucks during transport on the haul road and deposited in the nearby area. The mean cadmium concentrations in moss and subsurface soil throughout the entire study were 1.86 and 0.27 mg/kg dry weight, respectively. Cadmium concentrations in moss and subsurface soil were 0.08–24.30 and 0.07–0.75 mg/kg dry weight. There did not appear to be a connection between the elevated subsurface cadmium levels and the local geochemistry. Geospatial analysis showed that areas as far as 12 km north of the haul road may be affected by mining emission depositions (Hasselbach et al. 2005). In the vicinity of a smelter in Helena, Montana, average soil values were 72 ppm within 1 km and 1.4 ppm between 18 and 60 km (EPA 1981a). Total cadmium concentrations in soil samples taken from a Superfund site in southeast Kansas ranged from 15 to 86 mg/kg (ppm). In the same study, soil samples were extracted with diethylenetriamine-pentaacetic acid (DPTA) to approximate the plant-available metal concentrations. Extractable cadmium concentrations ranged from 0.6 to 10 mg/kg (ppm) (Abdel-Saheb et al. 1994). Soil cadmium levels in five Minnesota cities were highest in areas with the most vehicular traffic (>2 ppm in about 10% of inner-city samples) and also showed a pattern consistent with past deposition from a sewage-sludge incinerator (Mielke et al. 1991). Cadmium levels >750 mg/kg have been found in sites polluted by nonferrous metal mining and smelting have been reported (Alloway and Steinnes 1999).

In the Spring River Basin of Kansas, Missouri, and Oklahoma, part of the Tri-State Mining District, cadmium was detected in surface waters at concentrations of <1.0–24 µg/L (peak flow) and <1.0–75.0 µg/L (base flow). Cadmium was detected in the sediment of the sampling sites at concentrations ranging from 0.62 to 300 µg/g dry weight in the <250 µm sediment fraction and from 0.89 to 180 µg/g dry weight in the <63 µm fraction (Angelo et al. 2007). A study conducted in 1999 at the Patroon Creek

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Reservoir in Albany County, New York sampled sediment cores for heavy metals, including cadmium. The watershed includes two industrial sites: one in operation from 1955 to present and the other operating from 1958 to 1984. Sediment samples in the interval of 0–1.68 m showed an average cadmium concentration of 1.69 mg/kg. This concentration is comparable to other stream and reservoir sediments impacted by industrial pollution (Arnason and Fletcher 2003). Sediments of the Sawmill River in Yonkers, New York contained the highest cadmium levels (6.9 mg/kg) in the Hudson River Basin during a sampling study conducted between 1992 and 1995 (USGS 1998b).

Surficial sediments collected from 18 locations in three major tributaries to Newark Bay, New Jersey, had a mean cadmium concentration of 10 ± 6 mg/kg (ppm) dry weight (Bonnevie et al. 1994). The highest cadmium concentrations were found in the Ironbound section of the Passaic River, a heavily industrialized area (29 mg/kg and 14 mg/kg), and in the Arthur Kill on the northwest side of Prall's Island (15 mg/kg). An investigation of metals distribution in sediments along the Hudson River estuary revealed that cadmium concentrations in suspension were higher than in the bottom sediments by a factor of 30 (Gibbs 1994).

Soils derived from dredged material in confined disposal facilities in the Great Lakes Region had cadmium concentrations (dry weight) of <1.9 –32 ppm (Beyer and Stafford 1993). In an analytical survey of sewage sludges from 16 large cities in the United States, cadmium concentrations ranged from 2.72 to 242 ppm (dry weight). Besides the sample with a cadmium concentration of 242 ppm, all other sludges had cadmium contents ≤ 14.7 ppm (Gutenmann et al. 1994).

6.4.4 Other Environmental Media

Cadmium levels in food can vary greatly depending on the type of food, agricultural and cultivating practices, and amount atmospheric deposition and other anthropogenic contamination. In general, leafy vegetables, such as lettuce and spinach, and staples, such as potatoes and grains, contain relatively high values of cadmium. Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium. Meat and fish contain lower amounts of cadmium, with the exception of animal organ meats, such as kidney and liver, as these organs concentrate cadmium (Morrow 2001).

As part of the U.S. Food and Drug Administration (FDA) Total Diet Study, average concentrations of cadmium in 14 food groups were analyzed from samples collected in 56 American cities. Cadmium was found in nearly all samples at varying concentrations. In general, the eggs, milk and cheese, condiments

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and sweeteners, beverages, and fats and dressings groups contained low concentrations of cadmium (≤ 0.004 mg/kg) (FDA 2010). Food items that contained high levels of cadmium were dry roasted peanuts (0.054 mg/kg), shredded wheat cereal (0.050 mg/kg), boiled spinach (0.124 mg/kg), iceberg lettuce (0.051 mg/kg), leaf lettuce (0.064 mg/kg), and potato chips (0.057 mg/kg) (FDA 2010). [Table 6-3](#) summarizes the data from this study.

Watanabe et al. (1996) measured the cadmium content in rice samples from various areas in the world during the period from 1990 to 1995. Twenty-nine samples collected in the United States had a geometric mean of 7.43 ng Cd/g, with a standard deviation of 2.11. Shellfish, liver, and kidney meats have higher concentrations than other fish or meat (up to 1 ppm) (Elinder 1985a; IARC 1993; Schmitt and Brumbaugh 1990). Particularly high concentrations of cadmium of 2–30 mg/kg (ppm) fresh weight have been found in the edible brown meat of marine shellfish (Elinder 1992). Cadmium concentrations up to 8 $\mu\text{g/g}$ in oysters and 3 $\mu\text{g/g}$ in salmon flesh have been reported (IARC 1993). Sprague (1986) reviewed tissue concentrations of cadmium for marine mollusks and crustaceans. They found that drills, a type of sea snail, were higher in cadmium (average, 26 $\mu\text{g/g}$ dry weight) than almost all other mollusks, although scallops and whelks also tended to be high. Oysters from polluted areas averaged 18 $\mu\text{g/g}$ dry weight, which was significantly higher than oysters from clean areas (average concentration 1.4 $\mu\text{g/g}$ dry weight). Clams were relatively low in cadmium (average, 0.5–1.0 $\mu\text{g/g}$ dry weight). The average concentration of cadmium in clams from polluted areas was only 2.7 $\mu\text{g/g}$ dry weight, but this was significantly higher than levels in clams from clean areas. In Fiscal Year (FY) 1985/1986, the FDA conducted a survey of cadmium, lead, and other elements in fresh clams and oysters collected from U.S. coastal areas used for shellfish production (Capar and Yess 1996). Average cadmium levels (wet weight) were 0.09 ± 0.06 mg/kg (ppm) ($n=75$) in hardshell clams, 0.05 ± 0.04 mg/kg ($n=59$) in softshell clams, 0.51 ± 0.31 mg/kg ($n=104$) in Eastern oysters, and 1.1 ± 0.6 mg/kg ($n=40$) in Pacific oysters. In FY91, FDA analyzed 5 samples of domestic clams and 24 samples of domestic oysters (collected from both coasts) for cadmium and found average concentrations of 0.06 and 0.62 mg/kg, respectively (Capar and Yess 1996). Although no conclusions can be drawn in light of the small numbers of FY91 samples, these results do not appear to be appreciably different from those of the FY85/86 survey..

Cadmium is accumulated mainly in the hepatopancreas (digestive gland) of the crab, and cadmium levels as high as 30–50 ppm have been detected in this edible part of the animal. Cadmium levels as high as 10 ppm also have been measured in some species of wild-growing edible mushrooms (Lind et al. 1995). Lind et al. (1995) conducted a feeding study in mice to determine the bioavailability of cadmium from crab hepatopancreas and mushroom in relation to organic cadmium. The cadmium accumulation in the

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Table 6-3. Mean Concentrations of Cadmium for FDA's Total Diet Study Market Baskets 2006-1 through 2008-4

Food product	Mean concentration range (mg/kg)
Milk and cheese	Not detected–0.002
Eggs	Not detected–0.0003
Meat, poultry, and fish	Not detected–0.069
Legumes and nuts	0.001–0.054
Grain products	0.0001–0.028
Fruit	Not detected–0.015
Vegetables	0.001–0.124
Mixed dishes and meals	0.003–0.021
Desserts	Not detected–0.028
Condiments and sweeteners	0.001–0.0002
Fats and dressings	Not detected–0.004
Beverages	Not detected–0.001
Infant and junior foods	0.0002–0.026

Source: FDA 2010

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liver and kidney of the mice was used as an estimate of the intestinal absorption. The group that was fed crab accumulated less cadmium in the liver and kidney than the groups fed mushrooms or inorganic cadmium salt. They concluded from the results of the study that cadmium from boiled crab has a lower bioavailability for absorption in the gastrointestinal tract of mice than inorganic cadmium and cadmium from dried mushrooms. Almost all (99%) of the cadmium in the boiled crab hepatopancreas was associated with insoluble ligands, probably denatured protein. In fresh crab hepatopancreas, most of the cadmium is in a soluble form bound to metallothionein (Lind et al. 1995).

Significant concentrations of cadmium have been observed in fish living in stormwater ponds in Florida, especially in the redear sunfish, a bottom feeder (Campbell 1994). The mean cadmium concentration in redear sunfish living in stormwater ponds was 1.64 mg/kg wet weight compared to 0.198 mg/kg for redear sunfish living in control ponds. Similarly, the mean cadmium concentration in largemouth bass living in stormwater ponds was 3.16 mg/kg wet weight compared to 0.241 mg/kg for largemouth bass living in control ponds. Red drum, flounder, and seatrout collected from South Carolina estuaries during the period 1990–1993 had consistently low cadmium levels throughout the sampling area and with respect to species (Mathews 1994). The mean concentration for all fillets and whole fish was 86.2 ppb wet weight, with 70.7% (n=164) of the samples having <25 ppb.

Cadmium and other heavy metals were detected in several of the freshwater invertebrates and fish of two Maryland streams. Due to their remote location and lack of source inputs, it is believed that the cadmium contamination was a result of long-range atmospheric deposition. Samples were taken from the Herrington Creek tributary (HCRT) and Blacklick Run (BLK) during October 1997, April 1998, and July 1998. Cadmium concentrations in the trout of BLK ranged from about 37 to 90 ng/g wet, with the older specimens having the higher cadmium concentrations. Cadmium concentrations in crayfish ranged from about 40 to 160 ng/g wet in BLK, with the younger specimens containing the highest levels of cadmium. Crayfish in HCRT ranged from 45 to 155 ng/g, with the highest levels in the middle age group. In crayfish, cadmium strongly accumulates in the gills, while the kidney accumulates cadmium in trout (Mason et al. 2000).

Cadmium concentrations in the fish of the mining-contaminated waters of Oklahoma were reported by Brumbaugh et al. (2005). This area was part of the Tri-State Mining District that was extensively mined for lead and zinc from the mid-1800s to the 1950s, and contains nonremediated sites. Blood and carcass cadmium concentrations differed between species and sites, but were generally greatest in carp. Carcass cadmium in catfish were relatively low, with <0.1 µg/g dry weight in 34 of 36 samples.

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Cadmium concentrations of ≥ 0.5 ppm have been found in rice grown in cadmium-polluted areas of Japan (Nogawa et al. 1989) and China (Shiwen et al. 1990). Tobacco also concentrates cadmium from the soil, and cadmium content of cigarettes typically ranges from 1 to 2 $\mu\text{g}/\text{cigarette}$ (Elinder 1985a, 1992).

Some food crops, including confectionery sunflowers, have a propensity to take up cadmium from the soil in which they are grown and deposit it in the kernels. In a study to determine the cadmium burden of persons who report regular consumption of sunflower kernels, Reeves and Vanderpool (1997) analyzed 19 different lots of sunflower kernels from the 1995 crop grown in the northern Great Plains region of North Dakota and Minnesota. They found a range of 0.33–0.67 $\mu\text{g Cd/g}$, with a mean \pm standard deviation of 0.48 ± 0.11 $\mu\text{g/g}$ fresh weight. The study showed that high intakes of sunflower kernels increased the intake of cadmium. However, the amount of cadmium in whole blood or in red blood cells was not affected by cadmium intake. The authors pointed out that an increased intake of sunflowers will increase not only the cadmium intake, but also the intake of copper and phytate. In turn, this could reduce the availability of cadmium from this food source.

DOI (1985) examined the concentrations of cadmium in a variety of aquatic and terrestrial flora and fauna and identified six trends: (1) in general, marine biota contained significantly higher cadmium residues than their freshwater or terrestrial counterparts; (2) cadmium tends to concentrate in the viscera of vertebrates, especially in the liver and kidneys; (3) cadmium concentrations are higher in older organisms than in younger ones, especially in carnivores and marine vertebrates; (4) higher concentrations for individuals of a single species collected at various locations are almost always associated with proximity to industrial/urban areas or point-source discharges of cadmium-containing wastes; (5) background levels of cadmium in crops and other plants are generally < 1.0 mg/kg (ppm); and (6) cadmium concentrations in biota are dependent upon the species analyzed, the season of collection, ambient cadmium levels, and the sex of the organism.

During a study monitoring cadmium levels in 331 cigarette packs from over 20 areas around the world it was found that the mean cadmium level per cigarette was 1.15 $\mu\text{g}/\text{cigarette} \pm 0.43$ (AM \pm ASD) or 1.06 $\mu\text{g}/\text{cigarette} \pm 1.539$ (geometric mean [GM] \pm geometric standard deviation [GSD]). Cigarettes from Mexico had the highest mean level of cadmium with an AM \pm ASD of 2.03 $\mu\text{g}/\text{cigarette} \pm 0.33$ or a GM \pm GSD of 2.00 $\mu\text{g}/\text{cigarette} \pm 1.190$. Cigarettes from India had the lowest mean levels of cadmium with an AM \pm ASD of 0.35 $\mu\text{g}/\text{cigarette} \pm 0.09$ or a GM \pm GSD of 0.34 $\mu\text{g}/\text{cigarette} \pm 1.284$. The arithmetic

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mean for the United States was $1.07 \mu\text{g}/\text{cigarette} \pm 0.11$ and the $\text{GM} \pm \text{GSD}$ was $1.06 \mu\text{g}/\text{cigarette} \pm 1.115$ (Watanabe et al. 1987).

The cadmium content of coals varies widely; concentrations of $0.01\text{--}180 \mu\text{g}/\text{g}$ (ppm) have been reported for the United States (Thornton 1992; Wilber et al. 1992).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to cadmium through ingestion of food and drinking water, inhalation of particulates from ambient air or tobacco smoke, or ingestion of contaminated soil or dust. For nonsmokers, food is the major source of cadmium exposure (NTP 2005). Inhalation of cigarette smoke is the major source of cadmium exposure for smokers (CDC 2005). Cadmium is introduced to the food chain through agricultural soils, which may naturally contain cadmium, or from anthropogenic sources such as atmospheric deposition or direct application methods such as phosphate fertilizer application and municipal waste composting (Alloway and Steinnes 1999; Morrow 2001). Cadmium-plated utensils and galvanized equipment used in food processing and preparation; enamel and pottery glazes with cadmium-based pigments; and stabilizers used in food-contact plastics are also sources of food contamination (Galal-Gorchev 1993). Cadmium levels in soils are not a direct indicator of the level of cadmium in the food supply, with the exception of extreme contamination, as other factors such as the type of crop and farming methods are important (Morrow 2001).

Based on food intake rates and food-cadmium concentrations, the estimated geometric mean daily intake of cadmium for the U.S. population is $18.9 \mu\text{g}/\text{day}$, down from an estimated $30 \mu\text{g}/\text{day}$ in the 1980s (Choudhury et al. 2001; Gartrell et al. 1986). Based on the mean cadmium daily intakes for males and females aged 6–60 years reported by Choudhury et al. (2001), age-weighted mean cadmium intakes of $0.35 \mu\text{g}/\text{kg}/\text{day}$ for males and $0.30 \mu\text{g}/\text{kg}/\text{day}$ for females were calculated for U.S. nonsmokers.

In the Fourth National Report on Human Exposures to Environmental Chemicals reported by the CDC (2011) results from the National Health and Nutrition Examination Survey (NHANES) 1999–2008 were reported. Cadmium levels in blood (see Table 6-4), urine (creatinine corrected) (see Table 6-5), and urine (see Table 6-6) was evaluated for a variety age groups and ethnicities. Blood cadmium reflects both recent and cumulative exposures and urinary cadmium reflects cadmium exposure and the concentration of cadmium in the kidneys.

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Table 6-4. Geometric Mean and Selected Percentile Blood Concentrations (µg/L) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Total, age 1 and older	1999–2000	0.412 (0.378–0.449)	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.900–1.00)	1.30 (1.20–1.40)	7,970
	2001–2002	Not calculated	0.300 (<LOD–0.300)	0.400 (0.400–0.500)	0.900 (0.900–1.10)	1.30 (1.20–1.60)	8,945,
	2003–2004	0.304 (0.289–0.320)	0.300 (0.300–0.300)	0.500 (0.500–0.600)	1.10 (1.00–1.20)	1.60 (1.50–1.60)	8,372
	2005–2006	0.310 (0.294–0.327)	0.270 (0.250–0.280)	0.501 (0.460–0.560)	1.02 (0.910–1.13)	1.53 (1.34–1.75)	8,407
	2007–2008	0.315 (0.300–0.331)	0.270 (0.260–0.280)	0.500 (0.460–0.560)	1.00 (0.900–1.13)	1.51 (1.30–1.77)	8,266
Age group							
1–5 Years	1999–2000	Not calculated	<LOD	0.300 (<LOD–0.300)	0.400 (0.300–0.400)	0.400 (0.300–0.400)	723
	2001–2002	Not calculated	<LOD	<LOD	<LOD	0.300 (<LOD–0.300)	898
	2003–2004	Not calculated	<LOD	<LOD	0.200 (0.200–0.300)	0.200 (0.200–0.400)	910
	2005–2006	Not calculated	<LOD	<LOD	<LOD	0.230 (0.210–0.250)	968
	2007–2008	Not calculated	<LOD	<LOD	0.210 (<LOD–0.230)	0.240 (0.220–0.260)	817
6–11 Years	1999–2000	Not calculated	<LOD	0.300 (<LOD–0.300)	0.400 (0.300–0.400)	0.400 (0.400–0.500)	905
	2001–2002	Not calculated	<LOD	<LOD	<LOD	0.400 (0.300–0.400)	1,044
	2003–2004	Not calculated	<LOD	0.200 (<LOD–0.200)	0.300 (0.200–0.300)	0.300 (0.300–0.300)	856
	2005–2006	Not calculated	<LOD	<LOD	0.220 (0.200–0.300)	0.260 (0.230–0.280)	934
	2007–2008	Not calculated	<LOD	<LOD	0.230 (0.210–0.240)	0.260 (0.240–0.280)	1,011
12–19 Years	1999–2000	0.333 (0.304–0.366)	0.300 (<LOD–0.300)	0.300 (0.300–0.400)	0.800 (0.600–0.900)	1.10 (0.900–1.10)	2,135
	2001–2002	Not calculated	<LOD	0.300 (<LOD–0.300)	0.400 (0.400–0.500)	0.800 (0.600–1.10)	2,231
	2003–2004	Not calculated	0.200 (<LOD–0.200)	0.300 (0.300–0.300)	0.600 (0.500–0.700)	0.900 (0.800–1.10)	2,081
	2005–2006	Not calculated	<LOD	0.250 (0.240–0.270)	0.520 (0.500–0.700)	0.960 (0.820–1.08)	1,996
	2007–2008	Not calculated	<LOD	0.260 (0.240–0.270)	0.520 (0.400–0.670)	0.960 (0.730–1.19)	1,074

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Table 6-4. Geometric Mean and Selected Percentile Blood Concentrations (µg/L) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
≥20 Years	1999–2000	0.468 (0.426–0.513)	0.400 (0.300–0.400)	0.600 (0.600–0.700)	1.00 (1.00–1.10)	1.50 (1.40–1.60)	4,207
	2001–2002	Not calculated	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.10 (0.900–1.20)	1.60 (1.30–1.80)	4,772
	2003–2004	0.378 (0.359–0.398)	0.400 (0.300–0.400)	0.600 (0.600–0.700)	1.20 (1.20–1.30)	1.80 (1.60–1.90)	4,525
	2005–2006	0.373 (0.352–0.395)	0.330 (0.310–0.350)	0.610 (0.570–0.660)	1.17 (1.06–1.26)	1.72 (1.53–1.95)	4,509
	2007–2008	0.376(0.354–0.399)	0.330 (0.310–0.350)	0.600 (0.550–0.670)	1.16 (1.02–1.30)	1.70 (1.50–1.96)	5,364
Gender							
Males	1999–2000	0.403 (0.368–0.441)	0.400 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.900–1.10)	1.30 (1.20–1.50)	3,913
	2001–2002	Not calculated	0.300 (<LOD–0.300)	0.400 (0.400–0.500)	0.900 (0.900–1.10)	1.40 (1.20–1.80)	4,339
	2003–2004	0.283 (0.266–0.300)	0.300 (0.200–0.300)	0.500 (0.500–0.500)	1.10 (1.00–1.20)	1.60 (1.50–1.60)	4,131
	2005–2006	Not calculated	0.240 (0.220–0.260)	0.470 (0.420–0.530)	1.02 (0.910–1.12)	1.53 (1.27–1.86)	4,092
	2007–2008	0.299 (0.283–0.317)	0.240 (0.230–0.260)	0.470 (0.420–0.540)	1.05 (0.930–1.19)	1.60 (1.30–1.90)	4,147
Females	1999–2000	0.421 (0.386–0.460)	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.800–1.00)	1.30 (1.10–1.40)	4,057
	2001–2002	Not calculated	0.300 (0.300–0.400)	0.500 (0.500–0.600)	1.00 (0.900–1.10)	1.40 (1.20–1.60)	4,606
	2003–2004	0.326 (0.300–0.300)	0.300 (0.300–0.300)	0.600 (0.500–0.600)	1.10 (1.00–1.20)	1.60 (1.50–1.70)	4,241
	2005–2006	0.329 (0.311–0.349)	0.290 (0.280–0.310)	0.530 (0.480–0.580)	1.02 (0.870–1.18)	1.54 (1.33–1.79)	4,315
	2007–2008	0.331 (0.316–0.348)	0.290 (0.280–0.310)	0.530 (0.480–0.570)	0.980 (0.860–1.10)	1.43 (1.29–1.63)	4,119
Race/ethnicity							
Mexican Americans	1999–2000	0.395 (0.367–0.424)	0.400 (0.300–0.400)	0.400 (0.400–0.500)	0.700 (0.700–0.900)	1.10 (0.900–1.30)	2,742
	2001–2002	Not calculated	<LOD	0.300 (0.300–0.400)	0.600 (0.500–0.700)	1.00 (0.700–1.30)	2,268
	2003–2004	0.235 (0.26–0.255)	0.200 (0.200–0.300)	0.400 (0.300–0.400)	0.600 (0.500–0.800)	1.00 (0.800–1.50)	2,085
	2005–2006	Not calculated	0.220 (0.200–0.240)	0.350 (0.300–0.400)	0.580 (0.510–0.680)	0.820 (0.710–1.00)	2,236
	2007–2008	Not calculated	0.220 (0.210–0.230)	0.350 (0.320–0.370)	0.570 (0.510–0.660)	0.870 (0.690–1.02)	1,712

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Table 6-4. Geometric Mean and Selected Percentile Blood Concentrations (µg/L) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Non-Hispanic blacks	1999–2000	0.393 (0.361–0.427)	0.300 (0.300–0.400)	0.600 (0.500–0.600)	1.00 (0.800–1.10)	1.40 (1.10–1.50)	1,842
	2001–2002	Not calculated	<LOD	0.400 (0.400–0.500)	1.00 (0.900–1.00)	1.40 (1.20–1.50)	2,219
	2003–2004	0.304 (0.275–0.337)	0.300 (0.300–0.300)	0.500 (0.400–0.600)	1.00 (0.900–1.20)	1.50 (1.30–1.70)	2,292
	2005–2006	0.307 (0.290–0.326)	0.260 (0.250–0.280)	0.490 (0.440–0.570)	1.03 (0.880–1.21)	1.50 (1.23–1.79)	2,193
	2007–2008	0.333 (0.316–0.352)	0.280 (0.270–0.300)	0.550 (0.480–0.620)	1.20 (1.02–1.36)	1.81 (1.45–2.13)	1,746
Non-Hispanic whites	1999–2000	0.376 (0.470–0.209)	0.400 (0.300–0.400)	0.500 (0.500–0.600)	1.00 (0.900–1.10)	1.30 (1.20–1.40)	2,716
	2001–2002	Not calculated	<LOD	0.500 (0.500–0.600)	0.900 (0.900–1.10)	1.40 (1.20–1.80)	3,806
	2003–2004	0.313 (0.296–0.331)	0.300 (0.300–0.300)	0.600 (0.500–0.600)	1.10 (1.00–1.20)	1.60 (1.50–1.70)	3,478
	2005–2006	0.321 (0.300–0.343)	0.270 (0.250–0.300)	0.540 (0.470–0.610)	1.08 (0.930–1.23)	1.64 (1.40–1.94)	3,310
	2007–2008	0.210 (0.303–0.341)	0.270 (0.260–0.290)	0.520 (0.470–0.580)	1.05 (0.920–1.20)	1.55 (1.30–1.80)	3,461

^aThe proportion of results below the LOD was too high to provide a valid result.

CI = confidence interval; LOD = limit of detection

Source: CDC 2011

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Table 6-5. Geometric Mean and Selected Percentile Urine Concentrations (Creatinine Corrected) ($\mu\text{g/g}$ Creatinine) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Total, age 6 and older	1999–2000	0.181 (0.157–0.209)	0.219 (0.199–0.238)	0.423 (0.391–0.446)	0.712 (0.645–0.757)	0.933 (0.826–1.07)	2,257
	2001–2002	0.199 (0.181–0.218)	0.212 (0.194–0.232)	0.404 (0.377–0.440)	0.690 (0.630–0.754)	0.917 (0.813–0.998)	2,689
	2003–2004	0.210 (0.201–0.219)	0.208 (0.189–0.226)	0.412 (0.381–0.438)	0.678 (0.650–0.716)	0.940 (0.833–1.04)	2,543
	2005–2006	0.189 (0.169–0.210)	0.180 (0.160–0.200)	0.370 (0.310–0.430)	0.650 (0.590–0.720)	0.910 (0.770–1.08)	2,576
	2007–2008	0.193 (0.177–0.210)	0.190 (0.180–0.210)	0.370 (0.330–0.410)	0.660 (0.580–0.740)	0.960 (0.850–1.06)	2,627
Age group							
6–11 Years	1999–2000	Not calculated	0.085 (0.063–0.107)	0.147 (0.123–0.182)	0.210 (0.171–0.316)	0.300 (0.184–0.607)	310
	2001–2002	0.075 (0.059–0.094)	0.100 (0.083–0.112)	0.166 (0.136–0.192)	0.233 (0.206–0.281)	0.291 (0.221–0.440)	368
	2003–2004	0.090 (0.078–0.104)	0.091 (0.075–0.104)	0.126 (0.111–0.156)	0.200 (0.147–0.350)	0.308 (0.178–0.415)	287
	2005–2006	0.081 (0.072–0.092)	0.080 (0.070–0.090)	0.130 (0.110–0.140)	0.170 (0.150–0.190)	0.200 (0.180–0.240)	355
	2007–2008	0.084 (0.076–0.092)	0.080 (0.080–0.090)	0.120 (0.110–0.140)	0.180 (0.150–0.240)	0.260 (0.180–0.430)	394
12–19 Years	1999–2000	0.071 (0.051–0.098)	0.093 (0.084–0.106)	0.147 (0.130–0.163)	0.215 (0.204–0.240)	0.283 (0.222–0.404)	648
	2001–2002	0.078 (0.067–0.091)	0.091 (0.085–0.101)	0.136 (0.123–0.143)	0.191 (0.175–0.234)	0.280 (0.234–0.321)	762
	2003–2004	0.086 (0.077–0.096)	0.084 (0.074–0.097)	0.122 (0.113–0.135)	0.176 (0.154–0.198)	0.234 (0.187–0.274)	724
	2005–2006	0.076 (0.071–0.081)	0.080 (0.070–0.0990)	0.120 (0.110–0.130)	0.50 (0.140–0.180)	0.210 (0.160–0.240)	701
	2007–2008	0.070 (0.062–0.079)	0.070 (0.070–0.080)	0.110 (0.100–0.110)	0.150 (0.130–0.160)	0.180 (0.160–0.200)	376
≥ 20 Years	1999–2000	0.267 (0.247–0.289)	0.288 (0.261–0.304)	0.484 (0.433–0.545)	0.769 (0.727–0.818)	1.07 (0.927–1.17)	1,299
	2001–2002	0.261 (0.236–0.289)	0.273 (0.247–0.303)	0.481 (0.426–0.518)	0.776 (0.691–0.850)	0.979 (0.874–1.12)	1,559
	2003–2004	0.268 (0.255–0.281)	0.270 (0.247–0.292)	0.490 (0.444–0.538)	0.767 (0.688–0.830)	1.02 (0.909–1.14)	1,532
	2005–2006	0.240 (0.216–0.267)	0.250 (0.200–0.260)	0.440 (0.400–0.500)	0.730 (0.660–0.820)	1.02 (0.850–1.18)	1,520
	2007–2008	0.247 (0.227–0.270)	0.250 (0.220–0.270)	0.430 (0.390–0.70)	0.740 (0.670–0.840)	1.05 (0.930–1.16)	1,857

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-5. Geometric Mean and Selected Percentile Urine Concentrations (Creatinine Corrected) ($\mu\text{g/g}$ Creatinine) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Gender							
Males	1999–2000	0.154 (0.131–0.182)	0.174 (0.158–0.191)	0.329 (0.293–0.382)	0.617 (0.537–0.700)	0.788 (0.696–0.929)	1,121
	2001–2002	0.159 (0.143–0.177)	0.168 (0.157–0.182)	0.334 (0.304–0.364)	0.532 (0.491–0.653)	0.757 (0.690–0.856)	1,334
	2003–2004	0.173 (0.161–0.187)	0.162 (0.143–0.185)	0.325 (0.300–0.352)	0.591 (0.560–0.631)	0.740 (0.678–0.795)	1,277
	2005–2006	0.160 (0.145–0.177)	0.150 (0.130–0.160)	0.300 (0.260–0.340)	0.362 (0.560–0.340)	0.820 (0.710–0.990)	1,271
	2007–2008	0.160 (0.146–0.175)	0.160 (0.140–0.180)	0.290 (0.260–0.330)	0.520 (0.430–0.650)	0.740 (0.600–0.960)	1,327
Females	1999–2000	0.211 (0.170–0.261)	0.267 (0.239–0.308)	0.473 (0.423–0.551)	0.783 (0.690–0.917)	1.09 (0.813–1.38)	1,136
	2001–2002	0.245 (0.216–0.278)	0.263 (0.228–0.297)	0.479 (0.414–0.541)	0.792 (0.687–0.884)	0.985 (0.876–1.16)	1,355
	2003–2004	0.252 (0.238–0.266)	0.253 (0.227–0.288)	0.487 (0.438–0.533)	0.802 (0.716–0.906)	1.06 (0.940–1.21)	1,266
	2005–2006	0.220 (0.193–0.252)	0.220 (0.180–0.250)	0.420 (0.370–0.470)	0.690 (0.590–0.850)	0.990 (0.780–1.31)	1,305
	2007–2008	0.231 (0.211–0.254)	0.230 (0.200–0.270)	0.440 (0.390–0.480)	0.770 (0.700–0.860)	1.09 (0.970–1.17)	1,300
Race/ethnicity							
Mexican Americans	1999–2000	0.175 (0.137–0.223)	0.181 (0.144–0.225)	0.331 (0.266–0.418)	0.612 (0.441–0.828)	0.843 (0.674–1.13)	780
	2001–2002	0.156 (0.136–0.177)	0.170 (0.150–0.184)	0.282 (0.263–0.340)	0.501 (0.388–0.614)	0.693 (0.507–0.839)	682
	2003–2004	0.160 (0.147–0.181)	0.159 (0.140–0.183)	0.296 (0.256–0.311)	0.531 (0.418–0.667)	0.718 (0.562–0.950)	614
	2005–2006	0.162 (0.146–0.181)	0.150 (0.140–0.170)	0.280 (0.220–0.340)	0.480 (0.430–0.510)	0.570 (0.520–0.640)	652
	2007–2008	0.162 (0.144–0.183)	0.160 (0.130–0.180)	0.280 (0.220–0.340)	0.530 (0.390–0.640)	0.720 (0.520–1.07)	515
Non-Hispanic blacks	1999–2000	0.183 (0.140–0.240)	0.201 (0.168–0.241)	0.414 (0.343–0.472)	0.658 (0.516–0.827)	0.873 (0.722–0.962)	546
	2001–2002	0.190 (0.156–0.232)	0.195 (0.174–0.225)	0.385 (0.336–0.449)	0.676 (0.559–0.850)	0.917 (0.725–1.08)	667
	2003–2004	0.190 (0.173–0.210)	0.185 (0.168–0.207)	0.338 (0.288–0.431)	0.700 (0.500–0.818)	0.865 (0.708–1.10)	717
	2005–2006	0.171 (0.159–0.183)	0.160 (0.140–0.180)	0.320 (0.290–0.370)	0.550 (0.500–0.580)	0.700 (0.610–0.730)	692
	2007–2008	0.180 (0.164–0.197)	0.170 (0.160–0.190)	0.330 (0.290–0.390)	0.600 (0.470–0.700)	0.770 (0.690–0.900)	589

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-5. Geometric Mean and Selected Percentile Urine Concentrations (Creatinine Corrected) ($\mu\text{g/g}$ Creatinine) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Non-Hispanic whites	1999–2000	0.175 (0.146–0.209)	0.219 (0.191–0.250)	0.432 (0.387–0.470)	0.729 (0.666–0.783)	1.00 (0.826–1.16)	760
	2001–2002	0.205 (0.184–0.229)	0.224 (0.208–0.242)	0.421 (0.382–0.470)	0.719 (0.668–0.784)	0.931 (0.806–1.05)	1,132
	2003–2004	0.220 (0.209–0.235)	0.221 (0.197–0.253)	0.434 (0.398–0.476)	0.687 (0.647–0.767)	1.00 (0.830–1.08)	1,070
	2005–2006	0.193 (0.169–0.221)	0.180 (0.160–0.220)	0.390 (0.310–0.480)	0.680 (0.630–0.750)	0.930 (0.800–1.07)	1,041
	2007–2008	0.199 (0.178–0.221)	0.200 (0.180–0.220)	0.380 (0.340–0.440)	0.700 (0.630–0.810)	1.03 (0.880–1.13)	1,095

^aThe proportion of results below the LOD was too high to provide a valid result.

CI = confidence interval; LOD = limit of detection

Source: CDC 2011

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-6. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Total, age 6 and older	1999–2000	0.193 (0.169–0.220)	0.232 (0.214–0.249)	0.475 (0.436–0.519)	0.858 (0.763–0.980)	1.20 (1.06–1.33)	2,257
	2001–2002	0.210 (0.189–0.235)	0.229 (0.207–0.255)	0.458 (0.423–0.482)	0.839 (0.753–0.919)	1.20 (1.07–1.28)	2,690
	2003–2004	0.211 (0.196–0.226)	0.210 (0.200–0.230)	0.450 (0.400–0.500)	0.800 (0.730–0.880)	1.15 (0.980–1.26)	2,543
	2005–2006	0.191 (0.170–0.216)	0.200 (0.170–0.220)	0.400 (0.360–0.460)	0.780 (0.700–0.860)	1.05 (0.960–1.17)	2,576
	2007–2008	0.185 (0.173–0.198)	0.180 (0.170–0.200)	0.380 (0.360–0.400)	0.700 (0.50–0.770)	1.00 (0.920–1.12)	2,627
Age group							
6–11 Years	1999–2000	Not calculated	0.078 (0.061–0.101)	0.141 (0.115–0.173)	0.219 (0.178–0.233)	0.279 (0.211–0.507)	310
	2001–2002	0.061 (<LOD–0.081)	0.077 (0.067–0.092)	0.140 (0.112–0.160)	0.219 (0.184–0.262)	0.282 (0.260–0.326)	368
	2003–2004	0.077 (0.065–0.090)	0.080 (0.060–0.090)	0.120 (0.100–0.160)	0.190 (0.160–0.310)	0.310 (0.170–0.610)	287
	2005–2006	0.066 (0.056–0.078)	0.060 (0.050–0.080)	0.110 (0.090–0.130)	0.180 (0.130–0.240)	0.240 (0.160–0.290)	355
	2007–2008	0.064 (0.058–0.071)	0.060 (0.050–0.070)	0.110 (0.090–0.130)	0.180 (0.140–0.210)	0.230 (0.180–0.310)	394
12–19 Years	1999–2000	0.092 (0.067–0.126)	0.128 (0.107–0.148)	0.202 (0.183–0.232)	0.329 (0.272–0.372)	0.424 (0.366–0.596)	648
	2001–2002	0.109 (0.087–0.136)	0.135 (0.114–0.157)	0.210 (0.189–0.247)	0.327 (0.289–0.366)	0.442 (0.366–0.480)	762
	2003–2004	0.121 (0.190–0.134)	0.130 (0.110–0.150)	0.200 (0.160–0.190)	0.300 (0.260–0.360)	0.390 (0.330–0.490)	724
	2005–2006	0.099 (0.090–0.109)	0.110 (0.100–0.120)	0.170 (0.150–0.190)	0.240 (0.210–0.280)	0.310 (0.250–0.430)	701
	2007–2008	0.089 (0.079–0.100)	0.080 (0.070–0.110)	0.150 (0.140–0.170)	0.260 (0.200–0.300)	0.330 (0.280–0.410)	376
≥20 Years	1999–2000	0.281 (0.253–0.313)	0.306 (0.261–0.339)	0.551 (0.510–0.621)	0.979 (0.836–1.13)	1.31 (1.13–1.57)	1,299
	2001–2002	0.273 (0.249–0.299)	0.280 (0.261–0.308)	0.545 (0.493–0.607)	0.955 (0.855–1.06)	1.28 (1.20–1.43)	1,560
	2003–2004	0.260 (0.238–0.284)	0.210 (0.210–0.300)	0.260 (0.470–0.580)	0.890 (0.800–0.990)	1.25 (1.09–1.46)	1,532
	2005–2006	0.241 (0.213–0.272)	0.250 (0.220–0.290)	0.490 (0.440–0.560)	0.860 (0.790–0.930)	1.12 (1.06–1.32)	1,520
	2007–2008	0.232 (0.215–0.251)	0.240 (0.210–0.260)	0.450 (0.410–0.490)	0.790 (0.730–0.870)	1.13 (0.990–1.44)	1,857

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-6. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Gender							
Males	1999–2000	0.199 (0.165–0.241)	0.227 (0.193–0.263)	0.462 (0.381–0.539)	0.892 (0.748–1.15)	1.41 (0.980–1.83)	1,121
	2001–2002	0.201 (0.177–0.229)	0.223 (0.191–0.257)	0.445 (0.393–0.481)	0.870 (0.741–1.03)	1.22 (1.12–1.38)	1,335
	2003–2004	0.206 (0.190–0.222)	0.210 (0.190–0.230)	0.440 (0.390–0.490)	0.790 (0.700–0.870)	1.01 (0.890–1.25)	1,277
	2005–2006	0.195 (0.176–0.217)	0.210 (0.190–0.230)	0.400 (0.360–0.440)	0.800 (0.730–0.890)	1.17 (1.01–1.30)	1,271
	2007–2008	0.179 (0.162–0.197)	0.180 (0.160–0.200)	0.360 (0.320–0.400)	0.670 (0.540–0.780)	0.950 (0.800–1.14)	1,327
Females	1999–2000	0.187 (0.153–0.229)	0.239 (0.220–0.255)	0.492 (0.456–0.540)	0.806 (0.705–0.980)	1.10 (1.01–1.19)	1,136
	2001–2002	0.219 (0.192–0.251)	0.234 (0.202–0.265)	0.466 (0.433–0.519)	0.817 (0.733–0.886)	1.17 (0.918–1.36)	1,355
	2003–2004	0.216 (0.195–0.238)	0.210 (0.200–0.240)	0.450 (0.400–0.530)	0.820 (0.700–0.960)	1.20 (1.02–1.37)	1,266
	2005–2006	0.188 (0.160–0.221)	0.190 (0.170–0.200)	0.400 (0.350–0.480)	0.750 (0.640–0.860)	0.980 (0.830–1.20)	1,305
	2007–2008	0.191 (0.177–0.207)	0.190 (0.170–0.200)	0.400 (0.370–0.430)	0.740 (0.670–0.840)	1.09 (0.940–1.38)	1,300
Race/ethnicity							
Mexican Americans	1999–2000	0.191 (0.157–0.233)	0.202 (0.167–0.221)	0.438 (0.351–0.551)	0.813 (0.686–0.977)	1.12 (0.886–1.38)	780
	2001–2002	0.160 (0.135–0.189)	0.181 (0.171–0.198)	0.321 (0.285–0.362)	0.559 (0.430–0.733)	0.766 (0.633–1.15)	683
	2003–2004	0.175 (0.151–0.203)	0.170 (0.150–0.210)	0.350 (0.290–0.430)	0.680 (0.520–0.820)	1.04 (0.820–1.20)	614
	2005–2006	0.173 (0.152–0.193)	0.180 (0.160–0.200)	0.340 (0.300–0.380)	0.560 (0.500–0.630)	0.780 (0.660–0.900)	652
	2007–2008	0.160 (0.141–0.182)	0.170 (0.140–0.210)	0.320 (0.290–0.380)	0.570 (0.520–0.640)	0.730 (0.640–0.840)	515
Non-Hispanic blacks	1999–2000	0.283 (0.208–0.387)	0.312 (0.243–0.412)	0.633 (0.498–0.806)	1.22 (0.892–1.38)	1.48 (1.30–1.72)	546
	2001–2002	0.277 (0.229–0.336)	0.302 (0.257–0.354)	0.580 (0.476–0.713)	1.04 (0.843–1.38)	1.51 (1.28–1.74)	667
	2003–2004	0.265 (0.237–0.295)	0.270 (0.220–0.320)	0.550 (0.440–0.640)	0.960 (0.810–1.17)	1.52 (1.06–1.82)	717
	2005–2006	0.236 (0.240–0.210)	0.240 (0.210–0.260)	0.480 (0.420–0.530)	0.830 (0.670–0.930)	1.04 (0.870–1.26)	692
	2007–2008	0.246 (0.218–0.277)	0.260 (0.220–0.300)	0.460 (0.420–0.530)	0.840 (0.690–0.980)	1.40 (0.900–1.85)	589

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-6. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of Cadmium in the U.S. Population from 1999 to 2008

Group	Survey years	Geometric mean ^a (95% CI)	Selected percentiles (95% CI)				Sample size
			50 th	75 th	90 th	95 th	
Non-Hispanic whites	1999–2000	0.175 (0.148–0.206)	0.220 (0.194–0.246)	0.455 (0.388–0.510)	0.797 (0.714–1.01)	1.17 (0.963–1.47)	760
	2001–2002	0.204 (0.179–0.231)	0.221 (0.191–0.255)	0.445 (0.394–0.479)	0.813 (0.717–0.875)	1.17 (0.989–1.24)	1,132
	2003–2004	0.209 (0.192–0.226)	0.200 (0.190–0.220)	0.440 (0.390–0.500)	0.790 (0.700–0.860)	1.13 (0.940–1.26)	1,070
	2005–2006	0.185 (0.159–0.216)	0.200 (0.160–0.230)	0.400 (0.330–0.480)	0.780 (0.670–0.920)	1.05 (0.940–1.25)	1,041
	2007–2008	0.177 (0.161–0.195)	0.170 (0.150–0.190)	0.370 (0.330–0.400)	0.690 (0.620–0.780)	1.00 (0.880–1.12)	1,095

^aThe proportion of results below the LOD was too high to provide a valid result.

CI = confidence interval; LOD = limit of detection

Source: CDC 2011

6. POTENTIAL FOR HUMAN EXPOSURE

As a part of the New York City Health and Nutrition Examination Survey (NYC HANES), 2004 blood cadmium levels were evaluated in 1,811 New York City adults (age 20 years and older). The variables used in this study were sex, age, race/ethnicity, place of birth, family income, education, and smoking status (see Table 6-7 for detailed results of this study). The geometric mean blood cadmium concentration in New York City adults was 0.77 µg/L, slightly higher than the 1999–2000 estimated national mean of 0.47 µg/L with heavy smokers having the highest geometric mean blood cadmium level of 1.58 µg/L, higher than any other subgroup. The reason for the elevated blood cadmium levels in nonsmoking, New York City adults is not known, although it was speculated that higher shellfish consumption may be the cause of elevated blood cadmium levels in Asian subgroup (McKelvey et al. 2007).

Vahter et al. (1996) studied the dietary intake and uptake of cadmium in nonsmoking women consuming a mixed diet low in shellfish (n=34) or with shellfish once a week or more (n=17). The shellfish diets, with a median of 22 µg Cd/day, contained twice as much cadmium as the mixed diets, which had a median of 10.5 µg Cd/day. In spite of the differences in the daily intake of cadmium, there were no statistically significant differences in the blood cadmium concentrations of the shellfish group (0.25 µg/L) and the mixed diet group (0.23 µg/L) or in the urinary cadmium concentrations of the shellfish and mixed diet groups (0.10 µg/L in both groups). These results indicate a lower absorption of cadmium in the shellfish group than in the mixed diet group or a difference in kinetics. The authors suggested that a higher gastrointestinal absorption of cadmium in the mixed diet group could be explained in part by their lower body iron stores as measured by the concentrations of serum ferritin (S-fer). A median S-fer concentration of 18 µg/L was measured for the mixed diet group compared to a median of 31 µg/L for the shellfish group.

Except in the vicinity of cadmium-emitting industries or incinerators, the intake of cadmium from drinking water or ambient air is of minor significance (Elinder 1985a). Cadmium is removed from waste water and sewage through precipitation to hydroxide or carbonate compounds and ultimate separation (Schulte-Schrepping and Piscator 2002). EPA requires water suppliers to limit the cadmium concentration in water to <5 µg/L (EPA 2006a).

IARC (1993) reports that the total body burden of non-occupationally exposed adult subjects has been estimated to range from 9.5 to 50 mg in the United States and Europe. People living near sources of cadmium pollution may be exposed to higher levels of cadmium. Ambient air cadmium concentrations in industrialized areas was estimated between 15 and 150 ng/m³ (Morrow 2001). During a study conducted

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-7. Blood Cadmium Concentrations, Geometric Means, Adjusted Proportional Change in Means, and 95th Percentiles in New York City Adults in Population Subgroups

Variable	Number ^a	Results		
		Crude weighted geometric mean blood cadmium (µg/L)	Adjusted proportional change in mean blood cadmium (µg/L) ^b	Crude weighted 95 th percentile blood cadmium (µg/L)
Total:	1,811	0.77	—	1.88
Male	762	0.76	1.00	1.95
Female	1,049	0.79	1.07	1.83
20–39 years old	903	0.76	1.00	1.82
40–59 years old	673	0.84	1.16	2.19
≥60 years old	235	0.77	1.15	1.52
White, non-Hispanic ^c	529	0.73	1.04	1.71
Black, non-Hispanic ^c	390	0.80	1.11	1.97
Asian, non-Hispanic ^c	231	0.99	1.41	2.36
Hispanic ^c	630	0.73	1.00	1.73
Place of birth:				
United States	882	0.76	1.00	1.95
Outside the United States	923	0.79	1.02	1.73
Family income (\$ U.S.):				
<20,000	610	0.86	1.00	2.33
20,000–49,999	566	0.77	0.94	1.76
50,000–74,999	256	0.74	0.92	1.76
≥75,000	304	0.69	0.91	1.43
Education:				
<Bachelors	1,252	0.82	1.09	2.02
Bachelors or greater	551	0.69	1.00	1.43
Smoking status:				
Never smoked	1,036	0.66	1.00	1.28
Former smoker	310	0.71	1.07	1.32
Current smoker	449	1.22	1.88	3.00

^aTotals do not all equal 1,811 because of missing data.

^bThe exponential β coefficient from a log-linear multiple regression that includes all covariates in the table. Sample size for adjust analysis is 1,707, after excluding study participants for whom covariate data are missing.

^cExcludes 27 participants who self-classified as “other”.

Source: McKelvey et al. 2007

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in Germany between March and May 2000, cadmium levels in child-mother pairs, as a function of ambient air quality, were compared between populations in the urban, industrialized area of Duisburg and the rural area of North Rhine Westphalia. Cadmium levels in the ambient air of Duisburg-South ranged from 1.5 to 31 ng/m³, compared to 0.5 ng/m³ in the rural are of Westphalia. Cadmium levels in the blood and urine of mothers in the industrialized area were higher than in the rural areas. Cadmium levels in the blood and urine of the children did not differ between the two areas. In the industrialized area, regression analysis indicated a significant influence of cadmium in ambient air on cadmium in blood (Wilhelm et al. 2005).

It has been estimated that tobacco contains 1.7 µg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow 2001; NTP 2005). Tobacco leaves naturally accumulate large amounts of cadmium (Morrow 2001). During a study monitoring cadmium levels in 331 cigarette packs from over 20 areas around the world, it was found that the mean cadmium level per cigarette was 1.15 µg/cigarette ±0.43 (AM±ASD) or 1.06 µg/cigarette ±1.539 GM±GSD. Cigarettes from Mexico had the highest mean level of cadmium with an AM±ASD of 2.03 µg/cigarette ±0.33 or a GM±GSD of 2.00 µg/cigarette ±1.190. Cigarettes from India had the lowest mean levels of cadmium with an AM±ASD of 0.35 µg/cigarette ±0.09 or a GM±GSD of 0.34 µg/cigarette ±1.284 (Watanabe et al. 1987). The amount of cadmium absorbed from smoking one pack of cigarettes per day is about 1–3 µg/day (Lewis et al. 1972a; Nordberg et al. 1985), roughly the same as from the diet. This large contribution is due to the greater absorption of cadmium from the lungs than from the gastrointestinal tract (Elinder 1985a). Direct measurement of cadmium levels in body tissues confirms that smoking roughly doubles cadmium body burden in comparison to not smoking, with kidney concentrations averaging 15–20 µg/g wet weight for nonsmokers and 30–40 µg/g wet weight for heavy smokers at the age of 50–60 (Ellis et al. 1979; Hammer et al. 1973; Lewis et al. 1972a, 1972b). Ellis et al. (1979) found an increase in kidney cadmium of 0.11±0.05 mg per pack-year (AM±ASD) of smoking and an increase in liver cadmium concentration of 0.077±0.065 µg/g per pack-year (AM±ASD). Because excretion of cadmium is very slow, half-lives of cadmium in the body are correspondingly long (17–38 years) (Wester et al. 1992).

Workers in a variety of occupations may be exposed to cadmium and cadmium compounds. Occupations with potential exposure to cadmium are listed in [Table 6-8](#) (IARC 1993).

Highest levels of occupational exposure would be expected to occur in operations involving heating cadmium-containing products by smelting, welding, soldering, or electroplating, and also in operations associated with producing cadmium powders (OSHA 1990). The primary route of occupational exposure

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Table 6-8. Occupations with Potential Exposure to Cadmium and Cadmium Compounds

Occupation	
Alloy production ^a	Phosphorous production
Battery production ^a	Pigment production and use ^a
Brazing	Plastics production ^a
Coating	Plating
Diamond cutting	Printing
Dry color formulation	Semiconductor and superconductor production
Electroplating	Sensors production
Electrical contacts production	Smelting and refining ^a
Enameling	Solar cells production
Engraving	Soldering
Glasswork	Stabilizer production
Laser cutting	Textile printing
Metallizing	Thin film production
Paint production and use	Transistors production
Pesticide production and use	Welding

^aActivity with high risk because atmospheric concentrations of cadmium are high and the number of workers employed is significant.

Source: IARC 1993

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is through inhalation of dust and fumes, and also incidental ingestion of dust from contaminated hands, cigarettes, or food (Adamsson et al. 1979).

Concentrations of airborne cadmium found in the workplace vary considerably with the type of industry and the specific working conditions. Processes that involve high temperatures can generate cadmium oxide fumes that are absorbed very efficiently through the lungs (IARC 1993). Deposition and absorption of dust containing different compounds depend upon particle size (IARC 1993). These exposures can be controlled through use of personal protective equipment and good industrial hygiene practices, and through operating procedures designed to reduce workplace emissions of cadmium (OSHA 1990).

Data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace during the same period (NIOSH 1990); these data are summarized in [Table 6-9](#). The NOES database does not contain information on the frequency, level, or duration of exposure of workers to any of the chemicals listed. It provides only estimates of workers potentially exposed to the chemicals.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are most likely to be exposed to cadmium in from ingestion of food (NTP 2005). There are no data on gastrointestinal absorption of cadmium in children, although very limited evidence exists that cadmium absorption from the gut may be greater in young animals. Oral absorption is discussed in more detail in Section 3.4.1.2. A study performed in Cincinnati, Ohio, investigated cadmium in human milk

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Table 6-9. Estimated Number of Workers Potentially Exposed to Various Chemicals in the Workplace in 1981–1983

Chemical	Number of workers potentially exposed
Cadmium sulfide	45,562
Cadmium oxide	15,727
Cadmium (pure)	335
Cadmium dust (form unknown)	3,893
Cadmium powder (form unknown)	486
Cadmium sulfate	1,313
1:1 Cadmium salt of carbonic acid	164
Cadmium (form unknown)	88,968
Total	153,486

Source: NIOSH 1990

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and found a mean concentration of 19 ppb (0.019 ppm) (Jensen 1983). The NHANES 1999–2008 reported cadmium levels in blood (see Table 6-4) and urine (see Tables 6-5 and 6-6) for children in different age groups (CDC 2011). The NYC HANES did not test for blood cadmium levels in children, although the blood cadmium levels in adults were slightly higher than the national average (McKelvey et al. 2007). Results of the U.S. FDA Total Diet Study (Capar and Cunningham 2000) reported cadmium levels in infant and junior foods ranged from no detection to 0.090 mg/kg. According to the National Human Exposure Assessment Survey (NHEXAS), children in EPA Region V (Great Lakes Region) have a mean dietary cadmium exposure of 17 (± 1.8) $\mu\text{g/kg}$ for minority children and 21 (± 2.2) $\mu\text{g/kg}$ for non-minority children (Pellizzari et al. 1999).

Except in the vicinity of cadmium-emitting industries or incinerators, the intake of cadmium from drinking water or ambient air is of minor significance (Elinder 1985a). Ambient air cadmium concentrations in industrialized areas has been estimated between 15 and 150 ng/m^3 (Morrow 2001). Cadmium levels in the ambient air of Duisburg-South, Germany ranged from 1.5 to 31 ng/m^3 , compared to 0.5 ng/m^3 in the rural area of Westphalia. Cadmium levels in the blood and urine of mothers in the industrialized area were higher than in the rural areas. Cadmium levels in the blood and urine of the children did not differ between the two areas. In the industrialized area, regression analysis indicated a significant influence of cadmium in ambient air on cadmium in blood (Wilhelm et al. 2005). Children in the homes of parents who smoke also can be exposed to cadmium through the inhalation of environmental tobacco smoke. There is potential for cadmium originating from second-hand smoke to settle onto surfaces; thus, there is a possibility that children may ingest cadmium from contaminated surfaces by the hand-to-mouth pathway. Although no data were found, children playing near hazardous waste sites could be exposed to cadmium in soil by hand-to-mouth activity and/or soil pica. No case studies were found on accidental poisoning of children by swallowing cadmium-containing batteries or by ingesting cadmium-containing household pesticides, which also are potential routes of exposure. No information was found concerning differences in the weight-adjusted intakes of cadmium by children.

In the Workers' Home Contamination Study conducted under the Workers' Family Protection Act (DHHS 1995), several studies were identified that reported home contamination with cadmium originating from parental occupation in a lead smelter. In a study of 396 children of ages 1–9 years living <900 m from a primary lead smelter, 380 children (96%) had blood cadmium (CdB) levels $>0.0089 \mu\text{g/L}$ (Carvalho et al. 1986). The geometric mean and standard deviation were 0.087 $\mu\text{mol/L}$ and 2.5, respectively. No significant relationship was found between parental occupation in the smelter and CdB in children, but a significant relationship was found between presence of smelter dross in the house and

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elevated CdB in children. Higher CdB was significantly associated with shorter distance from the home to the smelter. In a similar study of 263 children (ages 1–9 years), living <900 m from a primary lead smelter, the mean cadmium in hair was significantly higher at 6.0 ppm for children whose fathers worked in lead smelters than the concentration of 3.7 ppm for children whose fathers had other jobs (Carvalho et al. 1989). In a study of 9 children from families of lead workers and 195 children (ages 4–17 years) from other families, the children from the families of lead workers had significantly higher geometric mean urinary cadmium (CdU) ($0.34 \mu\text{g/L} \pm 2.6$) than children from other families ($0.13 \mu\text{g/L} \pm 2.2$). The CdB levels of children from families of lead workers were higher than those of the children from other families, but the difference was not statistically significant (Brockhaus et al. 1988). Maravelias et al. (1989) measured the CdBs of 514 children (ages 5–12) from four schools located within various distances (500–1500 m) from a lead smelter. The geometric mean and geometric standard deviation CdB was $0.36 \mu\text{g/L} \pm 1.4$, respectively, with a range of 0.1–3.1 $\mu\text{g/L}$. Children from the school closest to the smelter had higher CdB levels than children from other schools, but no relationship was found between childrens' CdB and parental employment in the smelter.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). Baranowska (1995) also measured the concentrations of cadmium and lead in human placenta and in maternal and neonatal (cord) blood to assess the influence of a strongly polluted environment on the content of metals in tissues and on the permeability of the placenta to cadmium and lead. Samples for the study were collected from women living in the industrial district of Upper Silesia, one of the most polluted regions in Poland. The mean (range) concentration of cadmium in the air was 11.3 (2.1–25.4) ng/m^3 ($0.0113 [0.0021–0.0254] \mu\text{g/m}^3$). The mean concentrations of cadmium were 4.90 ng/mL ($0.00490 \mu\text{g/mL}$) in venous blood, 0.11 $\mu\text{g/g}$ in placenta, and 1.13 ng/mL ($0.00113 \mu\text{g/mL}$) in cord blood. The researcher concluded that the placenta is a better barrier for cadmium than for lead, based upon the relative decrease in metal concentrations from placenta to cord blood. The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein (Goyer and Cherian 1992). Timing and level

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of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies. Galicia-García et al. (1995) performed analyses of cadmium in maternal, cord, and newborn blood for 50 births in a Mexico City hospital. Multiple regression analyses applied to the data indicated a significant association between cord and newborn blood and between cord and maternal blood, but not among maternal and newborn blood. Birth weight of the newborns was found to be inversely associated with cord blood cadmium levels and smoking habits.

The analysis of Weidenberg et al. (2011) on the bioavailability of cadmium present in inexpensive jewelry suggests that substantial quantities of cadmium may be released from jewelry that is mouthed or swallowed and that the amount released was greatly varied from item to item.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The greatest potential for above-average exposure of the general population to cadmium is from smoking, which may double the exposure of a typical individual. Smokers who are exposed to cadmium in the workplace are at highest risk (CDC 2005). Individuals living near zinc or lead smelting operations, municipal incinerators, or other industrial processes emitting cadmium to the air will also have above-average exposure (Elinder 1985a). Exposures through inhalation are diminishing due to pollution controls at such facilities, but exposure resulting from soil contamination may continue to be significant. Persons who have corrosive drinking water and cadmium-containing plumbing, who habitually consume cadmium-concentrating foods (kidney, liver, and shellfish), or who ingest grains or vegetables grown in soils treated with municipal sludge or phosphate fertilizer all may have increased exposure (Elinder 1985a). The 2004 NYC HANES indicated that the New York City Asian population, especially those born in China, had higher concentrations of cadmium in blood. The authors speculate that this might be due to higher consumption of fish and shellfish (McKelvey et al. 2007).

Multiple pathways of exposure may exist for populations at hazardous waste sites contaminated with cadmium (ingestion of contaminated drinking water or garden vegetables, inhalation of airborne dust, incidental ingestion of contaminated soil).

Persons who consume large quantities of sunflower kernels can be exposed to higher levels of cadmium. Reeves and Vanderpool (1997) identified specific groups of men who were likely to consume sunflower kernels. The groups included baseball and softball players, delivery and long-distance drivers, and line workers in sunflower kernel processing plants.

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Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated waterbodies may be exposed to higher levels of cadmium associated with dietary intake (EPA 1993a). Cadmium contamination has triggered the issuance of several human health advisories. As of December 1997, cadmium was identified as the causative pollutant in five fish and shellfish consumption advisories in New York and another in New Jersey. EPA is considering including cadmium as a target analyte and has recommended that this metal be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. EPA recommends that residue data obtained from these monitoring programs be used by states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories for the protection of the general public as well as recreational and subsistence fishers. Under the same program, EPA has issued a statewide advisory in Maine for cadmium in moose (EPA 1998).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cadmium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cadmium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of cadmium and its salts are known well enough to permit estimation of the environmental fate of the compounds (Elinder 1985a, 1992). Additional information on properties does not appear to be crucial for evaluating potential fate.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2009, became available in February of 2011. This database is updated yearly and should provide a list of industrial production facilities and emissions.

The production volume, producers, import/export quantities, and uses of cadmium in the United States are well documented (SRI 2007; USGS 2007, 2008). Recycling of cadmium from spent batteries is increasing, and there are some data to suggest that there is still a large portion of cadmium being disposed of as municipal waste (USGS 2007). More data concerning the amount of municipal disposal would be helpful. Disposal of cadmium-containing wastes is regulated by the federal government, and data are available for industrial disposal practices (EPA 1982a; HSDB 2008; U.S. Bureau of Mines 1990). Most releases of cadmium are not from production of the metal or its compounds, but from combustion or smelter emissions, land application of sewage sludge and fertilizers, and other sources; estimates of these releases have been made (TRI09 2011).

Environmental Fate. Cadmium partitioning among media occurs, and this partitioning depends on local environmental conditions (Elinder 1985a, 1992). Cadmium may be subject to long-range transport in air and water (EPA 1980d). Cadmium is persistent in all media, although it may form organic complexes in soil and water under certain environmental conditions (EPA 1979). These processes, which are important for determining the environmental fate of cadmium, seem to be relatively well understood. Therefore, additional information on environmental fate does not appear to be essential to evaluate potential human exposure to cadmium.

Bioavailability from Environmental Media. Factors that control the bioavailability of cadmium from air, water, soil, and food have been investigated. Intestinal absorption of cadmium from food is low, about 5–10% (McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973), but the absorption of cadmium from soil is not known. Absorption from the lungs is somewhat greater, averaging about 25% (Nordberg et al. 1985). Estimates of dermal absorption of cadmium from soil and water on human skin have been made (Wester et al. 1992). There is some evidence that bioavailability of cadmium to plants and worms from contaminated soil is greater following remediation (Van Gestel et al. 1988). Additional information on the factors influencing bioavailability, particularly from remediated soil, are needed to assess residual risk to populations in the vicinity of reclaimed hazardous waste sites.

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Food Chain Bioaccumulation. Sufficient data are available to indicate that cadmium is concentrated in plants, aquatic organisms, and animals (Alloway et al. 1990; Beyer 1986; Handy 1992a, 1992b; Kuroshima 1992; Naqvi and Howell 1993; Roseman et al. 1994; Suresh et al. 1993; Vos et al. 1990). In vertebrates, cadmium accumulates in the liver and kidneys (Harrison and Klaverkamp 1990; Sileo and Beyer 1985; Vos et al. 1990). There is strong evidence for food chain bioaccumulation, but the potential for biomagnification is uncertain. Additional studies on biomagnification are needed to provide data for more accurate evaluation of the environmental impact of cadmium contamination.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of cadmium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of cadmium in the environment can be used in combination with the known body burden of cadmium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Current ambient air quality surveys testing for cadmium concentrations in rural and urban locations in the United States is lacking. Since the major source of exposure to cadmium is through dietary intake and since cadmium emissions to air are not expected to increase, there may be less interest in these data. There are several long-range atmospheric transport studies, but since these were conducted Europe and Russia, they only illustrate the potential for cadmium contamination via atmospheric deposition in the United States (Reimann et al. 1997; Shevchenko et al. 2003; Vidovic et al. 2005). There is also minimal data on current levels of cadmium in agricultural soils of the United States and the identification of the sources of cadmium levels, whether they are native geochemistry, phosphate fertilizers, atmospheric deposition, etc. (Xue et al. 2000). Continuing monitoring efforts in all media would allow more precise estimation of current sources and levels of human exposure and would assist in identifying major sources contributing to current exposure.

Exposure Levels in Humans. Cadmium has been detected in human blood, urine, breast milk, liver, kidney, and other tissues, both in occupationally exposed individuals and in the general population (CDC 2011; McKelvey et al. 2007; OSHA 1990). The NHANES and NYC HANES provide current data on the levels of cadmium in humans (CDC 2011; McKelvey et al. 2007). Other large-scale surveys concentrating on urban, agricultural, and suburban communities would be beneficial in understanding cadmium exposure to the U.S. population. Also, more information is needed on the specific exposure levels for different cadmium salts to determine if cadmium sulfides, for example, are associated with less harmful effects than cadmium oxides (Chettle and Ellis 1992).

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This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Cadmium has been measured in maternal and neonatal (cord) blood and in placenta (Baranowska 1995; Galicia-García et al. 1995; Kuhnert et al. 1982; Lauwerys et al. 1978; Roels et al. 1978; Truska et al. 1989), but the resulting data are sometimes conflicting with respect to the uptake of cadmium by the placenta. Research on the effects of timing and level of exposure on cadmium uptake by the placenta might help to explain these conflicting human studies. More recent data would be useful, both from women and children living in unpolluted areas (for background levels) and in polluted areas such as those near existing or former lead smelters.

There are some current data concerning cadmium exposure in children (Capar and Cunningham 2000; CDC 2011; Pellizzari et al. 1999). The NHANES 1999–2008 reported cadmium levels in blood (see [Table 6-4](#)) and urine (see [Table 6-5](#)) for children in different age groups (CDC 2011). The NYC HANES did not test for blood cadmium levels in children, although the blood cadmium levels in adults were slightly higher than the national average (McKelvey et al. 2007). Results of the U.S. FDA Total Diet Study (Capar and Cunningham 2000) reported cadmium levels in infant and junior foods ranged from no detection to 0.090 mg/kg. According to the NHEXAS, children in EPA Region V (Great Lakes Region) have a mean dietary cadmium exposure of 17 (± 1.8) $\mu\text{g/kg}$ for minority children and 21 (± 2.2) $\mu\text{g/kg}$ for non-minority children (Pellizzari et al. 1999).

Some body burden data are available for children living near lead smelters (Lagerkvist and Lundstrom 2004; Leroyer et al. 2001; Jin et al. 2002). However, none of the studies took place in the United States. Body burden data from children living in polluted and unpolluted regions (for background levels) of the United States are needed.

Current information on whether children are different in their weight-adjusted intake of cadmium via oral, inhalation, and dermal exposures was not located. A study to determine this information would be useful. Also, no information was found on childhood specific means to reduce cadmium exposure.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

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Exposure Registries. The State of New York has established the Heavy Metals Registry for surveillance of occupational heavy metals absorption. Cadmium levels $>10\text{ }\mu\text{g/L}$ in blood and $5\text{ }\mu\text{g/L}$ in urine are reported to the registry. The number of adults with reportable levels has varies per year, but there have always been <50 adults reported per year. Between 1995 and 2003, the number of reportable adults was <5 , and these exposures are due mostly to exposure for people working as jewelers and casting machine operators (NYS Dept of Health 2006).

No other exposure registries for cadmium were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in [Table 6-10](#).

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Table 6-10. Ongoing Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Birnbaum ER	Caldera Pharmaceuticals, Inc., Los Alamos, New Mexico	Biomarkers of response to environmental stressors	National Institute of Environmental Health Sciences
Chen Z	X-Ray Optical Systems, Inc. East Greenbush, New York	Direct measurement of trace elements in body fluids	National Center for Research Resources
Dweik BM	Giner, Inc., Newton, Massachusetts	Field-deployable monitor to assess personal exposure to multiple heavy metals	National Institute of Environmental Health Sciences
Fallin MD	Johns Hopkins University, Baltimore, Maryland	AGE-related epigenetic changes - environmental causes and disease consequences	National Institute of Environmental Health Sciences
Fox MA	Johns Hopkins University, Baltimore, Maryland	Environmental exposure to metal mixtures and kidney disease	National Institute of Environmental Health Sciences
Larkin PM	Ecoarray, Inc. Alachua, Florida	Developing and using sheephead minnow microarrays for ecotoxicology	National Institute of Environmental Health Sciences
Mo J	Kumetrix, Inc, Union City, California	Automatic multi-analyte in-situ bioassay for monitoring exposure to toxic metals	National Institute of Environmental Health Sciences
Polette-Niewold LA	Mayan Pigments, Inc.	SBIR phase II: One-step environmentally-friendly synthesis of novel organic/inorganic hybrid pigments	National Science Foundation
Santra S	University of Central Florida	Selective detection of toxic heavy metal ions using highly sensitive quantum dot probes	National Science Foundation
Basta N; Raun WR	Oklahoma State University	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Basta NT	Oklahoma State University	Heavy metal and trace element chemistry in soils: Chemical speciation and bioavailability	U.S. Department of Agriculture
Basta NT; Lower SK; Lanno R	Ohio State University	Heavy metal and trace element biogeochemistry in soils: Chemical speciation, bioavailability, and toxicity	U.S. Department of Agriculture
Bleam WF; Helmke PA	University of Wisconsin	Verifying and quantifying the specific complexation of metals to humic substances	U.S. Department of Agriculture
Chaney RL	Beltsville Agricultural Research Center	Characterization and remediation of potential trace element and phosphate risks from contaminated soils	U.S. Department of Agriculture
Chaney RL	Beltsville Agricultural Research Center	Risk assessment and remediation of soil and amendment trace elements	U.S. Department of Agriculture

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Table 6-10. Ongoing Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Chaney RL; Daniels WL	Virginia Polytechnic Institute	Effects of long-term biosolids applications on phytoavailability of soil cadmium and zinc	U.S. Department of Agriculture
Chang AC; Page AL	University of California, Riverside	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Eick MJ	Virginia Polytechnic Institute	Trace element and ligand adsorption/desorption from soil constituent surfaces	U.S. Department of Agriculture
Hopkins DG	North Dakota State University	Influence of geologic materials and pedogenic processes on trace elements in soil landscapes	U.S. Department of Agriculture
Hunt JR; Lykken GI	University of North Dakota	Whole body counting and radiotracer methods in research on mineral requirements in human nutrition	U.S. Department of Agriculture
Kpomblekou- Ademawou K; Ankumah RO	Tuskegee University	Trace elements in broiler littered soils: Fate and effects on nitrogen transformation	U.S. Department of Agriculture
Martinez CE	Pennsylvania State University	Chemical and biogeochemical processes involved in trace and toxic element cycling in soils	U.S. Department of Agriculture
Morrissey MT	Oregon State University	Characterization of the cadmium health risk, concentrations and ways to minimize cadmium residues in shellfish	U.S. Department of Agriculture
Schwab AP; Joern B; Johnston C	Purdue University	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Sparks DL	University of Delaware	Rates and mechanisms of metal and metalloid sorption/surfaces	U.S. Department of Agriculture
Thomas, DG; Kennedy TS	Oklahoma State University	Maternal dietary nutrients and neurotoxins in infant cognitive development	U.S. Department of Agriculture
Williams PL	University of Georgia	Environmental health impacts of soil contamination	U.S. Department of Agriculture
	National Risk Management Research Laboratory	Biomonitoring of source water quality	U.S. Environmental Protection Agency
Petterson L	National Exposure Research Lab Environmental Sciences Division Characterization and Monitoring Branch	Efficient monitoring of heterogeneous media and electronic wastes	U.S. Environmental Protection Agency

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Table 6-10. Ongoing Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Petterson L	National Exposure Research Lab Ecosystems Research Division Ecosystems Assessment Branch	Geochemical and interfacial applications for assessing ecological toxicant exposures	U.S. Environmental Protection Agency
Nolan P	Office of Regional Administrator Office of Environmental Measurement and Evaluation	Lower Merrimack River fish tissue study	U.S. Environmental Protection Agency
Janes D	Office of Research and Development National Health and Environmental Effects Research Lab Mid- Continent Ecology Division	Risks of heavy metals to aquatic organisms from multiple exposure routes	U.S. Environmental Protection Agency

Sources: FEDRIP 2008; SI/EPA 2007

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring cadmium, its metabolites, and other biomarkers of exposure and effect to cadmium. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

The most common analytical procedures for measuring cadmium concentrations in biological samples use the methods of atomic absorption spectroscopy (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP/AES). These basic methods of analysis are well defined and generally accepted for the analysis of cadmium.

Samples are prepared for AAS and ICP/AES methods in a variety of ways. Digestion with nitric acid is most common (Roberts and Clark 1986; Sharma et al. 1982). Cadmium in blood and plasma measured by graphite furnace atomic absorption spectroscopy (GFAAS) facilitated by a wet ashing pretreatment of samples resulted in good accuracy and reproducibility. The sample detection limit using this method was 0.4 µg/L (Roberts and Clark 1986). This method was also precise and highly reproducible in determining cadmium in whole blood, urine, and hair with 99–99.4% recoveries reported (Sharma et al. 1982). The matrix may also be modified with diammonium hydrogen phosphate or other agents such as palladium (Pd)-based modifiers (Moreira et al. 1995). Detection limits as low as 0.1 µg/L with recoveries ranging from 93 to 111% are reported using this technique (Subramanian and Meranger 1981; Subramanian et al. 1983). If the concentration of cadmium in the dissolved sample is below the detection limit, preconcentration techniques, such as chelation and extraction, may be employed (Gross et al. 1976; Sharma et al. 1982). Various ICP methods have been developed for measuring cadmium levels in biological materials. ICP dynamic reaction cell mass spectrometry (ICP-DRC-MS) has been shown to eliminate molybdenum-based polyatomic interferences, resulting in a reduction of observed urine cadmium concentrations, as compared to ICP-MS measurements (Jarrett et al. 2008). Since cadmium is a

7. ANALYTICAL METHODS

ubiquitous element, the risk of contamination during sampling, processing, and analysis must be minimized by strict laboratory procedures (Elinder and Lind 1985). In procedures for micro-determination, all glass and plastic-ware should be acid-washed and subsequently rinsed with double-distilled water.

Current analytical improvements deal primarily with the methods of sample preparation and sample introduction to the analytical systems in order to lower the detection limits or decrease sample analysis time. Various improvements in the methods of extraction, preconcentration, chelation, complexation, and sample introduction have been developed for use with biological media. Detection limits as low as 0.003 µg/L were reported (Espinosa Almendro et al. 1992; Cordero et al. 1994; Jeng et al. 1994; Katskov et al. 1994; Komárek et al. 1991; Ma et al. 1994b; Welz et al. 1991).

The cadmium concentration in biological samples may also be measured by a number of other methods such as radiochemical neutron activation analysis (RNAA). One RNAA procedure involving a rapid two-step solvent extraction was used for determining cadmium in tissue samples (Tandon et al. 1994). Another method to determine cadmium in biological materials is based on the ion-exchange scheme developed by SAMSAHL where cadmium is trapped on an anion exchange resin. With this method, recovery of 98% and a detection limit of 4 µg/kg were reported. The accuracy of the method was estimated by three different approaches: analysis using radiotracers in inactive sample solutions; by analyzing standards, pipetted on filter paper, and processed as samples; and determination by RNAA (Woittiez and Tangonan 1992).

Cadmium concentration in tissue may be measured both *in vivo* (Ellis 1985; Scott and Chettle 1986) and *in vitro* (Lieberman and Kramer 1970) by neutron activation analysis (NAA). Direct *in vivo* assessment of body burden in humans focused on the measurements of cadmium in the kidney and liver by NAA. The detection limits reported are approximately 2 mg cadmium for the total kidney and 1.5 µg/g for the liver (Ellis 1985); 1.9 mg cadmium for the kidney; and 1.3 µg/g for the liver (Scott and Chettle 1986).

X-ray fluorescence is also used for *in vivo* measurement of cadmium in the kidney (Christoffersson et al. 1987; Nilsson and Skerfving 1993; Scott and Chettle 1986; Skerfving and Nilsson 1992). The *in vivo* techniques are used for clinical measurements of individuals occupationally exposed to cadmium. Additional methods applicable to the analysis of cadmium in biological media include ICP/MS (Stroh 1993; Vanhoe et al. 1994), ICP/AES (Cordero et al. 1994; Espinosa Almendro et al. 1992), and high performance liquid chromatography (HPLC) (Chang and Robinson 1993; Steenkamp and Coetzee 1994).

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Electrothermal vaporization ICP/MS has been utilized for the analysis of dentin and enamel from teeth (Grünke et al. 1996). Electrochemical methods such as adsorptive cathodic stripping voltametry (ACSV) and potentiometric stripping analysis (PSA) have been applied to hair analysis (Zhang et al. 1993), animal tissues (LaBar and Lamberts 1994), and body fluids (Ostapczuk 1993).

Table 7-1 summarizes some of the methods used for sample preparation and analysis of cadmium in biological samples.

7.2 ENVIRONMENTAL SAMPLES

Analysis for cadmium in environmental samples is usually accomplished by AAS or AES techniques, with samples prepared by digestion with acid, preconcentrated with a chelating resin, or direct aspiration with no preparation (APHA 1977a, 1977b; EPA 1983a, 1983b, 1997b; OSHA 2002a, 2004; USGS 1985). Since cadmium in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, and subsequent analysis (APHA 1977a, 1977b; OSHA 2002a, 2002b). Inductively-coupled plasma spectrometry (ICP) analysis in standard methods is also popular. ICP analysis for water and air samples can be run in tandem with mass spectrometry (MS) or AES (EPA 1996b, 1997b, 2003; NIOSH 2003; OSHA 2002b). ACSV (Nimmo and Fones 1994), differential pulse anodic stripping voltametry (DP-ASV) (Nam et al. 1994), and epithermal NAA (Landsberger and Wu 1993) have also been used for air analysis. The accuracy of the analysis of cadmium in acid digested atmospheric samples, measured by ACSV, was evaluated and compared with GFAAS and ICP/MS.

Several methods standardized by EPA (1983a, 1983b, 1994b, 1996a, 1996b, 1997b, 2000, 2003) are used for measuring concentrations of cadmium in water. Techniques to compensate for chemical and matrix interferences in all three methods are described by EPA (1983a, 1983b, 1994b, 1996a, 1996b, 1997b, 2000, 2003). After soils and solid wastes are extracted or solubilized by acid digestion, they may be analyzed for cadmium by the same AAS methods that are used for water (EPA 1986d, 1986e). Water can also be analyzed for cadmium by NAA methods (Saleh et al. 1993), PSA methods (Ostapczuk 1993), and anodic stripping voltametry (ASV) (Daih and Huang 1992).

Sediment and soil samples have been analyzed for cadmium using the methods of GFAAS (Klemm and Bombach 1995). Preparation of the samples is generally accomplished by treatment with HCl and HNO₃.

7. ANALYTICAL METHODS

Table 7-1. Analytical Methods for Determining Cadmium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Digestion with nitric acid; chelation with APDC and extraction with MIBK	AAS	<1 ng/mL ^a	99	Sharma et al. 1982
Blood	Modification of matrix with diammonium hydrogen phosphate/Triton X-100	GFAAS	0.1 µg/L	100.8±4.3	Subramanian and Meranger 1981
Blood/plasma	Digestion with nitric acid; wet ashed	GFAAS	0.4 µg/L	No data	Roberts and Clark 1986
Serum	Dilution with ammonia/Triton X-100	ICP/MS	0.01 ng/mL	No data	Stroh 1993
Tissue and blood	Microwave digestion	FAAS/flow injection system	0.15 µg/L	No data	Welz et al. 1991
Human milk	Dilution with deionized and double distilled water	AAS	<0.01 ppb ^a	No data	Schulte-Lobbert and Bohn 1977
Hair	Digestion with nitric acid	AAS	0.07 µg/g ^a	99	Sharma et al. 1982
Kidney	None (<i>in vivo</i>)	XRF	170.1 µg/g	No data	Christoffersson et al. 1987
Kidney/liver	Chelation and extraction with solvent	AAS/direct aspiration	0.01 ppm ^a (liver) 1.9 mg (kidney)	No data	Gross et al. 1976
Kidney/liver	None (<i>in vivo</i>)	NAA	1.3 µg/g (liver) 1.9 mg (kidney)	No data	Scott and Chettle 1986
Muscle	Wet ashed with concentrated sulfuric acid	NAA	50 ppb	50–65	Lieberman and Kramer 1970
Urine	Dilution with nitric acid	ETAAS	0.045 µg/L	97–101	Komárek et al. 1991
Urine	Modification of matrix with diammonium hydrogen phosphate/nitric acid	GFAAS	0.09 ng/mL	92.7–111.1	Subramanian et al. 1983
Urine	Digestion with nitric acid	AAS	5.67 ng/mL ^a	99.4	Sharma et al. 1982
Biological materials	Microwave digestion followed by extraction with APTH in MIBK	ICP/AES	0.15 ng/mL	No data	Cordero et al. 1994
Biological materials	Extraction with 1,5-bis(di-2-pyridylmethylene) thiocarbonohydrazide in MIBK	ICP/AES	0.1 ng/mL	No data	Espinosa Almendro et al. 1992

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Table 7-1. Analytical Methods for Determining Cadmium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biological materials	Digestion with acid	GFAAS/flow injection system	0.003 µg/L	No data	Ma et al. 1994a
Biological fluids (blood, urine)	Acidification	PSA	0.001 µg/kg	No data	Ostapczuk 1993
Biological materials	Dry tissues; irradiation followed by acid digestion	RNAA	4 µg/kg	98	Woittiez et al. 1992
Teeth, dentin, and enamel	Digested in nitric acid, diluted with water	ETV-ICP-MS PN-ICP-MS	No data	No data	Grünke et al. 1996
Whole blood, urine	Modified with palladium based modifier	ETAAS	0.22 µg/L	No data	Moreira et al. 1995
Biological materials	Digested with nitric acid and hydrogen peroxide	B-9001-95; ICP-AES	No data	93	USGS 1996

^aLowest concentration found

AAS = atomic absorption spectroscopy; APDC = ammonium pyrrolidenedithiocarbamate; APTH = 1,3-bis-[1-(2-pyridyl)ethylidene] thiocarbon-hydride; ETAAS = electrothermal atomic absorption spectroscopy; FAAS = flame atomic absorption; GFAAS = graphite furnace atomic absorption; ICP/AES = inductively coupled plasma atomic emission spectroscopy; ICP/MS = inductively coupled plasma mass spectrometry; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; PSA = potentiometric stripping analysis; RNAA = radio chemical neutron activation analysis; XRF = x-ray fluorescence

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The most common method for analysis of cadmium in foods is AAS (Bruhn and Franke 1976; Dabeka 1979; Muys 1984), with GFAAS being one of the most common AAS methods used (Cabrera et al. 1995). The FDA's Total Diet Study 1991–1996 analyzed cadmium and other element concentrations in food by dry ash mineralization and GFAAS (Capar and Cunningham 2000). RNAA (Greenberg et al. 1979), differential pulse ASV (Satzger et al. 1982, 1984), and the calorimetric dithizone method (AOAC 1984) may also be employed. The AAS techniques appear to be most sensitive, with recoveries ranging from 94 to 109% (Bruhn and Franke 1976; Muys 1984). A method used to isolate cadmium by first extracting with bismuth diethyldithiocarbamate ($\text{Bi}[\text{DDC}]_3$) and then with zinc diethyldithiocarbamate ($\text{Zn}[\text{DDC}]_2$) in chloroform and then measuring by RNAA showed 94–106% recovery (Greenberg et al. 1979).

Table 7-2 summarizes some of the methods used for sample preparation and analysis of cadmium in environmental samples.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cadmium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cadmium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Measurements of cadmium in liver and kidney are all useful biological indices for human exposure to cadmium (Roels et al. 1981b). Human milk, human placentas, and maternal and neonatal

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Table 7-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on glass fiber filter; ashed with hydrochloric and nitric acids	Method 311; AAS	0.005 µg/m ³	90	APHA 1977b
Air	Collection on membrane filter; ashed with hydrochloric and nitric acids	Method 7048; AAS	0.05 µg per sample	No data	NIOSH 1994
Air	Collection on membrane filter; digestion with nitric acid and perchloric acid	Method 7300; ICP	0.3 ng/mL	99.8–105.2	NIOSH 2003
Air	Collection using filters, wipes, or bulk materials; desorbed with water extractions and mineral acid digestions	Method 121; AAS/AES	0.004 µg/mL	99.5	OSHA 2002a
Air	Collection on membrane filter; digested in nitric acid, sulfuric acid, and hydrogen peroxide	Method 125G; ICP-AES	0.14 µg ^a 0.47 µg ^b	No data	OSHA 2002b
Air	Collection on membrane filter; digested with nitric acid and small amounts of hydrochloric acid	Method 189; AAS/AAS-HGA	0.2 µg/m ³ (AAS) ^a 0.70 µg/m ³ (AAS) ^b 0.007 µg/m ³ (AAS-HGA) ^a 0.025 µg/m ³ (AAS-HGA) ^b	No data	OSHA 2004
Air	Collection on membrane filter, wipe, or bulk material; digest with nitric and hydrochloric acids	Method 206; ICP-AES	0.0062 µg/mL ^a 0.0205 µg/mL ^b	No data	OSHA 1991
Air	Irradiation UF filters	Epithermal NAA	8 ng	No data	Landsberger et al. 1993
Air (aerosols)	Acid digestion with filters	ACSV	0.6 ng/mL	100	Nimmo and Fones 1994
Atmospheric particles	Direct analysis	ETV-ICP-MS	pg/m ³ range	No data	Lüdke et al. 1997
Water	Digestion with nitric acid	Method 213.1; AAS/direct aspiration	5 µg/L	94±24	EPA 1983a
Water	Digestion with nitric acid	Method 213.2; AAS/GFAAS	0.1 µg/L	96–99	EPA 1983b

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Table 7-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	On-line preconcentration with ion exchange or sorbent extraction columns	GFAAS/ flow injection system	0.8 ng/L	No data	Welz et al. 1992
Water	Digestion with nitric acid	Method 1637; chelation and GFAAS	0.0075 µg/L	No data	EPA 1996a
Water	Digestion with nitric acid	Method 1638; ICP-MS	0.025 µg/L	No data	EPA 1996b
Water	Preconcentrated with chelating resin	Method 1640; Online Chelation/ ICP-MS	0.0024 µg/L	No data	EPA 1997b
Water	Digested with hydrochloric and nitric acids	Method 200.5; AVICP-AES	0.1 µg/L	98±1.1	EPA 2003
Water and Wastes	Digestion with acids	Method 200.7; ICP-AES	1 µg/L (aqueous); 0.2 mg/kg (solids)	82–98	EPA 1994a
Various	Digestion with nitric and hydrochloric acids	Method 6010C; ICP-AES	No data	97	EPA 2000
Water and sediments	No preconcentration or pretreatment	I-1135; AAS	10 µg/L	No data	USGS 1985
Water	Digested with whole water	I-4471-97; ICP-OES	5 µg/L	No data	USGS 1998a
Various	Direct aspiration with no preconcentration or pretreatment	I-5135; AAS	10 µg/L	No data	USGS 1985
Soil	Digestion with nitric acid	Method 7130; AAS/direct aspiration	0.005 mg/L	No data	EPA 1986e
Soil	Digestion with nitric acid	Method 7131; GFAAS	0.1 µg/L	No data	EPA 1986d
Soil and sediment	Ultrasonic slurry in dilute nitric acid	GFAAS	No data	100±10	Klemm and Bombach 1995

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Table 7-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment	Digestion with hydrochloric and nitric acid	LEAFS	500 fg	No data	Zhou et al. 1998
Soil and sediment	Digestion with hydrofluoric acid and nitric acid; complexation with DDPA using on-line sorbent extraction system	GFAAS/ flow injection system	0.8 µg/L	No data	Ma et al. 1994b
Food	Dry ashed; oxidization with nitric acid	ASV/ differential pulse	1 ng/g	99–108	Satzger et al. 1984
Food	Dry ashed; complexation with APCD; extraction with isoamyl acetate	AAS	0.1 ng/g	97.5±2.5	Bruhn and Franke 1976
Food	Extraction with Bi(DDC) ₃ then with Zn(DDC) ₂ in chloroform	RNAA	0.029 µg/g ^c	94–106	Greenberg et al. 1979
Food (24 hour diet)	Microwave digestion with nitric acid and hydrogen peroxide	GFAAS	0.004 µg/g	94–101	Yang et al. 1995
Food	Dry ashed; complexation with NaDDTC; extraction with IBMK	GFAAS	0.1 ppb ^c	94–109	Muys 1984
Food	Homogenization followed by wet ashing	GFAAS	0.01 ppb	94–108	Zhang et al. 1997
Fruit	Homogenized fruit slurried with zirconia	ETAAS	0.3 ng/g	97.7±0.3	Cabrera et al. 1995

^aQualitative detection limit^bQuantitative detection limit^cLowest concentration found

AAS = atomic absorption spectroscopy; ACSV = adsorptive cathodic stripping voltammetry; APCD = ammonium pyrrolidino carbodithioate; ASV = anodic stripping voltammetry; AVICP-AES = axially viewed inductively coupled plasma-atomic emission spectrometry; Bi(DDC)₃ = bismuth diethyldithiocarbamate; DDPA = ammonium diethyldithiophosphate; ETV-ICP-MS = electrothermal vaporization inductively coupled plasma mass spectrometry; GFAAS = graphite furnace atomic absorption; HGA = heated graphite atomizer; IBMK = isobutyl methyl ketone; ICP = inductively coupled plasma; LEAFS = laser-excited atomic fluorescence spectrometry; MS = mass spectrometry; NAA = neutron activation analysis; NaDDTC = sodiumdiethyl-dithiocarbamate; OES = optical emission spectroscopy; RNAA = radiochemical neutron activation analysis; Zn(DDC)₂ = zinc diethyldithiocarbamate

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blood have been investigated as means to determine exposures of women and infants to cadmium (Baranowska 1995; Abadin et al. 1997). Sensitive and selective methods are available for the detection and quantitation of cadmium in these biological materials (Elinder and Lind 1985; Sharma et al. 1982). Improved methods for sample preparation and *in vivo* analysis of liver and kidney content are needed to assist in monitoring environmentally exposed populations.

Effect. Sensitive methods are also available for measuring biological markers of cadmium effect, particularly urine or serum concentration of β 2-microglobulin, retinol-binding protein, metallothionein, and creatinine (Kawada et al. 1990; Roels et al. 1989; Topping et al. 1986).

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Cadmium is ubiquitous in the environment and does not degrade. It is found in air, water, soil, sediments, and food. Analytical methods exist for the analysis of cadmium in all of these environmental media, and these methods have the sensitivity to measure background levels and detect elevated concentrations due to anthropogenic sources such as hazardous waste sites (EPA 1983a, 1983b, 1994b, 1996a, 1996b, 1997b, 2000, 2003). Additional research to reduce chemical and matrix interferences are needed to improve the speed and accuracy of the analyses.

7.3.2 Ongoing Studies

The National Report on Human Health Exposure to Environmental Chemicals is an ongoing biomonitoring assessment conducted by CDC. This survey measures over 200 chemicals in blood and urine from random samples collected from participants in the National Health and Nutrition Examination Survey (NHANES). The National Exposure Report was last published in 2009 and an update of biomonitoring levels for some of the chemicals, including cadmium, was published in 2012 (CDC 2012).

The information in [Table 7-3](#) was found as a result of a search of the Federal Research in Progress database (FEDRIP 2008).

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Table 7-3. Ongoing Analytical Methods Studies on Cadmium

Investigator	Affiliation	Research description	Sponsor
Parker D	University of California	Isotopic dilution methods for probing the bioavailability of trace elements in soils and sediments	U.S. Department of Agriculture
Pierzynski G	Kansas State University	Chemistry, bioavailability, and toxicity of constituents in residuals and residual treated soils	U.S. Department of Agriculture
Schwab AP; Joern B; Johnston C	Purdue University	Chemistry and bioavailability of waste constituents in soils	U.S. Department of Agriculture
Santra S	University of Central Florida	Selective detection of toxic heavy metal ions using highly sensitive quantum dot probes	National Science Foundation
Swain G	Michigan State University	Diamond microelectrode arrays: New materials for the electrochemical detection of aqueous analytes	U.S. Department of Agriculture

Source: FEDRIP 2008

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of $0.03 \mu\text{g Cd/m}^3$ for cadmium. This MRL is based on a LOAEL of 0.088 mg Cd/m^3 (LOAEL_{HEC} of 0.01 mg Cd/m^3) for respiratory effects in rats exposed to cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995) and an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of $0.01 \mu\text{g Cd/m}^3$ for cadmium. This MRL is based on the 95% lower confidence limit of the urinary cadmium level associated with a 10% extra risk of low molecular weight proteinuria (UCDL₁₀) estimated from a meta-analysis of environmental exposure data. An air concentration that would result in this urinary cadmium level ($0.5 \mu\text{g/g creatinine}$), assuming a dietary cadmium intake of $0.3 \mu\text{g/kg/day}$, was estimated using biokinetic models. The estimated air concentration of $0.1 \mu\text{g Cd/m}^3$ was divided by an uncertainty factor of 3 for human variability and a modifying factor of 3.

The EPA has not established a reference concentration (RfC) for cadmium.

ATSDR has derived an intermediate-duration oral MRL of $0.5 \mu\text{g Cd/kg/day}$ for cadmium. This MRL is based on a BMDL_{std1} of $0.05 \text{ mg Cd/kg/day}$ for skeletal effects in young female rats exposed to cadmium chloride in drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of $0.1 \mu\text{g Cd/kg/day}$ for cadmium. This MRL is based on the UCDL₁₀ for low molecular weight proteinuria estimated from a meta-analysis of environmental exposure data. A cadmium intake that would result in the UCDL₁₀ ($0.5 \mu\text{g/g creatinine}$) at age 55 was estimated using pharmacokinetic models. The cadmium intake of $0.33 \mu\text{g/kg/day}$ was divided by an uncertainty factor of 3 for human variability.

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The EPA has established a reference dose (RfD) of 5×10^{-4} mg/kg/day in water and 1×10^{-3} mg/kg/day in food (IRIS 2012). The RfD is based on a chronic intake that would result in a kidney concentration of 200 µg/g ww.

The international and national regulations, advisories, and guidelines regarding cadmium in air, water, and other media are summarized in [Table 8-1](#).

Cadmium compounds are included on the list of 189 chemicals listed as hazardous air pollutants under Section 112 of the Clean Air Act as amended (EPA 2007). Cadmium also is on the list of chemicals appearing in the Emergency Planning and Community Right-To-Know Act of 1986 (EPA 2008g). Under Title III of this statute, owners and operators of facilities that manufacture, import, process, or otherwise use the chemicals on this list of report annually their release of those chemicals to any environmental media.

Cadmium and cadmium chloride are designed as hazardous substances under Section 311 of the Clean Water Act; any discharge of these chemicals over a specified threshold level into navigable waters is subject to reporting requirements (EPA 2008c).

Cadmium is a hazardous waste under the Resource Conservation and Recovery Act (RCRA) under several circumstances. Groundwater monitoring is required at municipal solid waste landfills (EPA 2008d) and cadmium is considered a priority persistent, bioaccumulative, and toxic (PBT) chemical under RCRA waste minimization chemical listing (EPA 1998).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2008
	Cadmium and cadmium compounds	Group 1 ^a	
WHO	Air quality guidelines		WHO 2000
	Cadmium ^{b,c}	5 ng/m ³	
	Drinking water quality guidelines		WHO 2004
	Cadmium	0.003 mg/L	
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	Biological exposure indices		ACGIH 2007
	Cadmium and inorganic compounds		
	Cadmium in urine	5 µg/g creatinine	
	Cadmium in blood	5 µg/L	
	TLV (8-hour TWA)		
	Cadmium	0.01 mg/m ³	
	Hazardous air pollutant		EPA 2007
	Cadmium compounds	Yes	42 USC 7412
NIOSH	REL (10-hour TWA)		NIOSH 2005
	Cadmium ^f	Potential occupational carcinogens	
	Cadmium oxide	Potential occupational carcinogens	
	IDLH		
	Cadmium (as Cd)	9 mg/m ³	
	Cadmium oxide (as Cd)	9 mg/m ³	
	Category of pesticides		NIOSH 1992b
	Cadmium carbonate	Group II pesticide ^g	
	Cadmium chloride	Group I pesticide ^h	
	Cadmium sulfate	Group II pesticide ^g	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
OSHA	PEL (8-hour TWA) for general industry		OSHA 2007a
	Cadmium (as Cd)	5 µg/m ³	29 CFR 1910.1027
	PEL (8-hour TWA) for shipyard industry		OSHA 2007b
	Cadmium (as Cd)	5 µg/m ³	29 CFR 1915.1027
	PEL (8-hour TWA) for construction industry		OSHA 2007c
	Cadmium (as Cd)	5 µg/m ³	29 CFR 1926.1127
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
	Cadmium chloride	Yes	
	Drinking water standards and health advisories		EPA 2011b
	Cadmium		
	1-day health advisory for a 10-kg child	0.04 mg/L	
	10-day health advisory for a 10-kg child	0.04 mg/L	
	DWEL	0.02 mg/L	
	Lifetime	0.005 mg/L	
	National primary drinking water standards		EPA 2009b
	Cadmium		
	MCL	0.005 mg/L	
	Public health goal	0.005 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008c 40 CFR 117.3
	Cadmium chloride	10 pounds	
	Toxic pollutants designated pursuant to Section 307(a)(1) of the Clean Water Act		EPA 2008h 40 CFR 401.15
	Cadmium and compounds	Yes	
c. Food			
FDA	Bottled drinking water		FDA 2007
	Cadmium	0.005 mg/L	21 CFR 165.110
	EAFUS	No data	FDA 2008

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Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Cadmium	A2 ^j	
	Cadmium compounds (as Cd)	A2 ^j	
EPA	Carcinogenicity classification		IRIS 2012
	Cadmium	Group B1 ^k	
	Inhalation unit risk		
	Cadmium	1.8x10 ⁻³ per µg/m ³	
	RfC		
	Cadmium	No data	
	RfD		
	Cadmium		
	Food	1x10 ⁻³ mg/kg-day	
	Water	5x10 ⁻⁴ mg/kg-day	
	RCRA waste minimization PBT priority chemical list		EPA 1998 63 FR 60332
	Cadmium	Yes	
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2008d 40 CFR 264, Appendix IX
	Cadmium	Yes	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008e 40 CFR 302.4
	Cadmium	Yes ^{l,m}	
	Cadmium and compounds	Yes ⁿ	
	Cadmium chloride	Yes ^o	
	Reportable quantity		
	Cadmium	10 pounds	
	Cadmium and compounds	None ^p	
	Cadmium chloride	10 pounds	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Cadmium

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting		EPA 2008g 40 CFR 372.65
	Cadmium	01/01/1987	
	Cadmium compounds ^g	01/01/1987	
	Extremely Hazardous Substances		EPA 2008f 40 CFR 355, Appendix A
	Cadmium oxide		
	Reportable quantity	100 pounds	
NTP	Threshold planning quantity	100/10,000 pounds	
	Carcinogenicity classification		NTP 2011
	Cadmium and cadmium compounds	Known to be human carcinogens	

^aGroup 1: The agent is carcinogenic to humans.

^bThe guideline value is based on the prevention of a further increase of cadmium in agricultural soils, which is likely to increase the dietary intake.

^cTWA based on effects other than cancer or odor/annoyance using an averaging time of 1 year.

^dRespirable fraction.

^eHigher current priority chemical for guideline development.

^fREL applies to all cadmium compounds (as Cd).

^gGroup II pesticide: Contains the pesticides that pose as significant risk of carcinogenic, teratogenic, neurotoxic, or reproductive effects

^hGroup I pesticide: Contains the pesticides that pose as significant risk of adverse acute health effects at low concentrations

ⁱThe CMC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed briefly without resulting in an unacceptable effect. The CCC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect.

^jA2: Suspected human carcinogen.

^kGroup B1: Probable human carcinogen based on limited evidence of carcinogenicity in humans.

^lDesignated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act.

^mNo reporting of releases of this hazardous substance is required if the diameter of the pieces of the solid metal released is larger than 100 micrometers (0.004 inches).

ⁿDesignated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act and Section 112 of the Clean Air Act.

^oDesignated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.

^pIndicates that no reportable quantity is being assigned to the generic or broad class.

^qCadmium compounds: Includes any unique chemical substance that contains cadmium as part of that chemical's infrastructure.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = Criteria Maximum Concentration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

10. GLOSSARY

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

10. GLOSSARY

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

10. GLOSSARY

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

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variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1^* —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

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Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose₍₅₀₎ (TD₅₀)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences (proposed), Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: September, 2012
Profile Status: Post-Public Comment Draft 2
Route: ☒ Inhalation ☐ Oral
Duration: ☒ Acute ☐ Intermediate ☐ Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.03 ☐ mg/kg/day ☒ $\mu\text{g Cd/m}^3$

Reference: NTP. 1995. Cadmium oxide administered by inhalation to F344/N rats and B6C3F1 mice. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC.

Experimental design: Groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/ m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/ m^3) 6.2 hours/day, 5 days/week for 2 weeks. The mean MMAD of the cadmium oxide particles was 1.5 μm with a geometric standard deviation of 1.6–1.8. The animals were observed twice daily and weighed on days 1 and 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates).

Effect noted in study and corresponding doses: All rats in the 8.8 mg Cd/ m^3 group died by day 6; no other deaths occurred. A slight decrease in terminal body weights was observed at 2.6 mg Cd/ m^3 ; however, the body weights were within 10% of control weights. Significant increases in relative and absolute lung weights were observed at 0.26 (males only), 0.88, and 2.6 mg Cd/ m^3 . Histological alterations were limited to the respiratory tract and consisted of alveolar histiocytic infiltrate and focal inflammation in alveolar septa in all rats exposed to ≥ 0.088 mg Cd/ m^3 , necrosis of the epithelium lining alveolar ducts in all rats exposed to ≥ 0.26 mg Cd/ m^3 , tracheobronchiolar lymph node inflammation at ≥ 0.88 mg Cd/ m^3 (incidences in the 0, 0.088, 0.26, 0.88, 2.6, and 8.8 mg Cd/ m^3 groups were 0/3, 0/5, 5/5, 5/5, and 3/4 in males and 0/4, 1/5, 1/5, 3/5, 5/5, and 3/5 in females), degeneration of the nasal olfactory epithelium at 0.88 mg Cd/ m^3 (0/5, 0/5, 0/5, 2/5, 5/5, and 5/5 in males and 0/5, 0/5, 0/5, 4/5, 4/5, and 4/4 in females) and inflammation (0/5, 0/5, 0/5, 1/5, 5/5, and 3/5 in males and 0/5, 0/5, 0/5, 0/5, 4/5, and 3/4 in females) and metaplasia (0/5, 0/5, 0/5, 1/5, 0/5, and 5/5 in males and 0/5, 0/5, 0/5, 0/5, 4/5, and 4/4 in females) of the nasal respiratory epithelium at 2.6 mg Cd/ m^3 .

Dose and end point used for MRL derivation: The LOAEL of 0.088 mg Cd/ m^3 was selected as the point of departure for derivation of the MRL; benchmark dose analysis was considered; however, the data were not suitable for benchmark dose analysis because the incidence data for alveolar histiocytic infiltration do not provide sufficient information about the shape of the dose-response relationship below the 100% response level.

☐ NOAEL ☒ LOAEL

Uncertainty Factors used in MRL derivation:

☒ 10 for use of a LOAEL

☒ 3 for extrapolation from animals to humans with dosimetric adjustment

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[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The LOAEL_{HEC} was calculated using the equations below.

$$\text{LOAEL}_{\text{HEC}} = \text{LOAEL}_{\text{ADJ}} \times \text{RDDR}$$

The duration-adjusted LOAEL (LOAEL_{ADJ}) was calculated as follows:

$$\begin{aligned}\text{LOAEL}_{\text{ADJ}} &= 0.088 \text{ mg Cd/m}^3 \times 6.2 \text{ hours/24 hours} \times 5 \text{ days/7 days} \\ \text{LOAEL}_{\text{ADJ}} &= 0.016 \text{ mg Cd/m}^3\end{aligned}$$

The regional deposited dose ratio (RDDR) for the pulmonary region of 0.617 was calculated with EPA's RDDR calculator (EPA 1994a) using the final body weight of 0.194 kg for the male rats exposed 0.088 mg Cd/m³, the reported MMAD of 1.5 µm and the midpoint of the reported range of geometric standard deviations (1.7)

$$\begin{aligned}\text{LOAEL}_{\text{HEC}} &= 0.016 \text{ mg Cd/m}^3 \times 0.617 \\ \text{LOAEL}_{\text{HEC}} &= 0.01 \text{ mg Cd/m}^3\end{aligned}$$

Was a conversion used from intermittent to continuous exposure? Yes (see above)

Other additional studies or pertinent information that lend support to this MRL: The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986b) estimated that an 8-hour exposure to 1–5 mg/m³ would be immediately dangerous.

Animal studies support the findings in humans that acute exposure to cadmium results in lung damage. Single exposures to approximately 1–10 mg Cd/m³ as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m³ 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). At lower concentrations of 0.4–0.5 mg Cd/m³ as cadmium oxide for 2–3 hours (Buckley and Bassett 1987b; Grose et al. 1987) or 0.17 mg Cd/m³ as cadmium chloride 6 hours/day for 10 days (Klimisch 1993) resulted in mild hypercellularity and increases in lung weight. Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m³ as cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m³ (NTP 1995). At similar concentrations (0.19 or 0.88 mg Cd/m³ as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1–2 hours (Graham et al. 1978; Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m³

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as cadmium carbonate for 2 hours (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m³ as cadmium oxide for 2 hours (Rusch et al. 1986).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: September, 2012
Profile Status: Post-Public Comment Draft 2
Route: ☒ Inhalation ☐ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Graph Key: 63
Species: Human

Minimal Risk Level: 0.01 ☐ mg/kg/day ☒ $\mu\text{g Cd/m}^3$

Reference: Buchet JP, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.

Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

Suwazono Y, Sand S, Vahter M, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Experimental design: As detailed in the chronic oral MRL worksheet, a meta-analysis of select environmental exposure dose-response studies examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of renal function in environmentally exposed populations was conducted; for the inhalation MRL, the meta-analysis also included dose-response data from three occupational exposure studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). The meta-analysis was used to establish a point of departure for the urinary cadmium-response relationship and pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) were used to predict cadmium air concentrations.

Dose and end point used for MRL derivation: Analysis of the available environmental exposure studies and occupational exposure studies resulted in an estimation of a urinary cadmium level that would result in a 10% increase in the prevalence of β_2 -microglobulin proteinuria (UCD_{10}). The lowest UCD_{10} (1.34 $\mu\text{g/g}$ creatinine) was estimated from the European environmental exposure studies (Buchet et al. 1990; Järup et al. 2000; Suwazono et al. 2006); the UCD_{10} values from the occupational exposure studies were 7.50 $\mu\text{g/g}$ creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 $\mu\text{g/g}$ creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). The UCD_{10} from the environmental exposure studies was selected as the basis of the MRL. The 95% lower confidence limit on this value (UCDL_{10}) of 0.5 $\mu\text{g/g}$ creatinine was used as the point of departure for the MRL.

☐ NOAEL ☐ LOAEL ☒ UCDL_{10}

Deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition, retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow, S; moderate, M; or fast, F). Cadmium compounds are classified as follows: oxides and hydroxides, S; sulfides, halides and nitrates, M; all other, including chloride salts, F.

Inhalation exposures ($\mu\text{g}/\text{m}^3$) to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μg (AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucocilliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Kjellström-Nordberg pharmacokinetic model (1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure.

An airborne cadmium concentration of 1.8–2.4 $\mu\text{g}/\text{m}^3$ as cadmium oxide or 1.2–1.4 $\mu\text{g}/\text{m}^3$ as cadmium sulfide would result in a urinary cadmium level of 0.5 $\mu\text{g}/\text{g}$ creatinine, assuming that the air was the only source of cadmium. This assumption is not accurate because the diet is a significant contributor to the cadmium body burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in nonsmoking males and females in the United States are 0.35 and 0.30 $\mu\text{g Cd/kg/day}$, respectively (0.32 $\mu\text{g/kg/day}$ for males and females combined) (Choudhury et al. 2001).

Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (AMAD=1 μm) and oral intakes that yield the same urinary cadmium level, exposure to an airborne cadmium concentration of 0.1 $\mu\text{g}/\text{m}^3$ and a dietary intake of 0.3 $\mu\text{g/kg/day}$ would result in a urinary cadmium level of 0.5 $\mu\text{g}/\text{g}$ creatinine.

Uncertainty Factors and Modifying Factors used in MRL derivation:

- ☐ 10 for use of a LOAEL
- ☐ 10 for extrapolation from animals to humans with dosimetric adjustment
- ☒ 3 for human variability

The uncertainty factor of 3 for human variability was used to account for the possible increased sensitivity of diabetics (Åkesson et al. 2005; Buchet et al. 1990).

☒ modifying factor of 3

The modifying factor of 3 was used to account for the lack of adequate human data that could be used to compare the relative sensitivities of the respiratory tract and kidneys.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? The pharmacokinetic model assumes continuous exposure.

Other additional studies or pertinent information that lend support to this MRL: Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations include an increase in residual volume in workers exposed to air concentrations of cadmium

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fumes ranging from 0.008 (in 1990) to 1.53 mg/m³ (in 1975) (mean urinary cadmium level in the workers was 4.3 µg/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034–0.156 mg/m³ (Davison et al. 1988); and decreased force vital capacity in workers exposed to >0.2 mg/m³ (Smith et al. 1976). Additionally, Chan et al. (1988) found significant improvements in several parameters of lung function of workers following reduction or cessation of cadmium exposure.

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as N-acetyl-β-glucosaminidase (NAG), amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate. The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight proteins (particularly, β2-microglobulin, retinol binding protein, and human complex-forming glycoprotein [pHC]) in cadmium workers, as compared to levels found in a reference group of workers or the general population (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Significant alterations in the prevalence of low molecular weight proteinuria among cadmium workers has been observed at urinary cadmium levels of 1.5 µg/g creatinine and higher (Chen et al. 2006a; Elinder et al. 1985a; Jakubowski et al. 1987; Järup and Elinder 1994).

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: September, 2012
Profile Status: Post-Public Comment Draft 2
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Graph Key: 33
Species: Rat

Minimal Risk Level: 0.5 ☒ $\mu\text{g Cd/kg/day}$ ☐ ppm

Reference: Brzóska MM, Moniuszko-Jakoniuk J. 2005d. Disorders in bone metabolism of female rats chronically exposed to cadmium. *Toxicol Appl Pharmacol* 202(1):68-83.

Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005a. Bone mineral density, chemical composition and biomechanical properties of the tibia of female rats exposed to cadmium since weaning up to skeletal maturity. *Food Chem Toxicol* 43(10):1507-1519.

Brzóska MM, Majewska K, Moniuszko-Jakoniuk J. 2005c. Weakness in the mechanical properties of the femur of growing female rats exposed to cadmium. *Arch Toxicol* 79(5):277-288.

Experimental design: Groups of 40 3-week-old female Wistar rats were exposed to 0, 1, 5, or 50 mg Cd/L as cadmium chloride in drinking water for 12 months. The investigators noted that cadmium intakes were 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day in the 1, 5, and 50 mg/L groups, respectively. Using cadmium intake data presented in a figure, cadmium intakes of 0.2, 0.5, and 4 mg Cd/kg/day were estimated. Bone mineral density, bone mineral concentration, and mineralization area of the lumbar spine, femur and total skeleton (bone mineral density only) were assessed after 3, 6, 9, or 12 months of exposure. The mechanical properties of the femur and tibia were evaluated after 12 months of exposure. Markers for bone resorption (urinary and serum levels of C-terminal cross-linking telopeptide of type I collagen [CTX]) and bone formation (serum osteocalcin, total alkaline phosphatase, and cortical bone and trabecular bone alkaline phosphatase), and serum and urinary levels of calcium were also measured at 3, 6, 9, and 12 months.

Effect noted in study and corresponding doses: No significant alterations in body weight gain or food and water consumption were observed. Significant decreases in total skeletal bone mineral density was observed at ≥ 0.2 mg Cd/kg/day; the decrease was significant after 3 months in the 4 mg Cd/kg/day group, after 6 months in the 0.5 mg Cd/kg/day group, and after 9 months in the 0.2 mg Cd/kg/day group. Significant decreases in whole tibia and diaphysis bone mineral density were observed at ≥ 0.2 mg Cd/kg/day after 12 months of exposure. At 0.2 mg Cd/kg/day, bone mineral density was decreased at the proximal and distal ends of the femur after 6 months of exposure; diaphysis bone mineral density was not affected. At 0.5 mg Cd/kg/day, bone mineral density was decreased at the femur proximal and distal ends after 3 months of exposure and diaphysis bone mineral density after 6 months of exposure. At 4 mg Cd/kg/day decreases in femoral proximal, distal, and diaphysis bone mineral density were decreased after 3 months of exposure. Similarly, bone mineral density was significantly decreased in the lumbar spine in the 0.2 and 0.5 mg Cd/kg/day groups beginning at 6 months and at 3 months in the 4 mg Cd/kg/day group. Significant decreases in the mineralization area were observed in the femur and lumbar spine of rats exposed to 4 mg Cd/kg/day; lumbar spine bone mineral area was also affected at 0.5 mg Cd/kg/day. Significant decreases in tibia weight and length were observed at 4 mg Cd/kg/day. In tests of the mechanical properties of the tibia diaphysis, significant alterations in ultimate load, yield load, and

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displacement at load were observed at ≥ 0.2 mg Cd/kg/day; work to fracture was also significantly altered at 4 mg Cd/kg/day. In the mechanical properties compression tests of the tibia, significant alterations were observed in ultimate load, ultimate load, and stiffness at 0.2 mg Cd/kg/day; displacement at yield and work to fracture at ≥ 0.5 mg Cd/kg/day; and displacement at ultimate at 4 mg Cd/kg/day. Multiple regression analysis showed that the cadmium-induced weakness in bone mechanical properties of the tibia was primarily due to its effects on bone composition, particularly the non-organic components, organic components, and the ratio of the ash weight to organic weight. The mechanical properties of the femur were strongly influenced by the bone mineral density (at the whole bone and diaphysis). A significant decrease in femur length was observed at 6 months of exposure to ≥ 0.2 mg Cd/kg/day; however, decreases in length were not observed at other time points in the 0.2 or 0.5 mg Cd/kg/day groups. Femur weight was significantly decreased at 4 mg Cd/kg/day. In tests of mechanical properties of the femoral neck and distal, decreases in yield load, ultimate load, displacement at ultimate, work to fracture (neck only), and stiffness (distal only) were observed at ≥ 0.2 mg Cd/kg/day. For the femoral diaphysis, significant alterations were observed for yield load, displacement at yield, and stiffness at ≥ 0.2 mg Cd/kg/day. Significant decreases in osteocalcin concentrations were observed in all cadmium groups during the first 6 months of exposure, but not during the last 6 months. Decreases in total alkaline phosphatase levels at 4 mg Cd/kg/day, trabecular bone alkaline phosphatase at 0.2 mg Cd/kg/day, and cortical bone alkaline phosphatase at 4 mg Cd/kg/day were observed. CTX was decreased at ≥ 0.2 mg Cd/kg/day. Total urinary calcium and fractional excretion of calcium were increased at ≥ 0.2 mg Cd/kg/day.

Dose and end point used for MRL derivation:

[] NOAEL [] LOAEL [X] BMDL_{sd1}

At the lowest dose tested, 0.2 mg Cd/kg/day, a number of skeletal alterations were observed including decreases in bone mineral density in the lumbar spine, femur, and tibia, alterations in the mechanical properties of the femur and tibia, decreases in osteocalcin levels, decreases in trabecular bone alkaline phosphatase, and decreases in CTX. Of these skeletal end points, the decrease in bone mineral density was selected as the critical effect because Brzóska et al. (2005a, 2005c) demonstrated that the bone mineral density was a stronger predictor of femur and tibia strength and the risk of fractures.

Available continuous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to data (Table A-1) for changes in bone mineral density of the femur and lumbar spine in female rats resulting from exposure to cadmium in the drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). The BMD and the 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest Akaike's information criterion (AIC) for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the benchmark dose software (BMDS) to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and non-constant variance are negative, then the data set is considered not to be suitable for BMD modeling.

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Table A-1. Data Sets for Changes in Mineral Bone Density of the Femur and Lumbar Spine in Female Rats Exposed to Cadmium in Drinking Water for 6, 9, or 12 Months

Dataset ^a	Dose (mg Cd/kg/day)			
	0	0.2	0.5	4
Femur ^b				
6 month	329.7±3.6	317.6±2.7 ^c	308.5±3.4 ^d	303.4±3.4 ^e
9 month	343.8±3.1	328.2±2.9 ^d	322.8±3.0 ^e	310.4±3.4 ^e
12 month	354.3±3.7	338.0±1.9 ^d	330.9±3.1 ^d	318.7±3.4 ^e
Lumbar spine ^b				
6 month	272.0±2.4	263.4±2.6 ^c	258.3±2.7 ^d	249.5±2.9 ^e
9 month	282.4±2.3	271.8±1.6 ^d	267.8±1.8 ^e	259.5±2.7 ^e
12 month	286.1±2.3	275.5±1.9 ^d	269.1±1.9 ^e	257.1±3.0 ^e

^an=10.

^bmean±SE; standard errors were transformed to standard deviations for benchmark dose modeling via a function in the BMD software.

^cSignificantly different (p≤0.05) from the control group.

^dSignificantly different (p≤0.01) from the control group.

^eSignificantly different (p≤0.001) from the control group.

Source: Brzóska and Moniuszko-Jakoniuk 2005d

The potential points of departures derived from the best fitting models for each dataset are summarized in Table A-2.

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Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models Predicting Changes in Bone Mineral Density in Female Rats After Cadmium Exposure From Drinking Water

Exposure Period (months)	Best-fitting model	Number of doses	BMD _{sd1} ^a (mg Cd/kg/day)	BMDL _{sd1} ^a (mg Cd/kg/day)
Femur				
6	Linear	3	0.24	0.17
9	Hill	4	0.11	0.05
12	Hill	4	0.09	0.05
Lumbar spine				
6	Hill	4	0.19	0.08
9	Hill	4	0.11	0.05
12	Hill	4	0.12	0.07

^aBMDs and BMDLs from continuous data are associated with a 1 standard deviation change from the control.

The BMDL_{sd1} of 0.05 mg Cd/kg/day estimated from the 9-month lumbar spine data set was selected as the point of departure for the MRL. In young female rats, the process of intense bone formation occurs during the first 7 months of life (the first 6 months of exposure in this study); thereafter, the increase in bone mineral density slows. In the lumbar spine of the control group, the changes in bone mineral density at 3–6 months, 6–9 months, and 9–12 months were 15, 4, and 1%, respectively. Thus, the 9-month data may best reflect the effect of cadmium on bone mineral density during the period of rapid skeletal growth. The lumbar spine data was selected over the femur data set because trabecular bone, which is abundant in the spine, appears to be more susceptible to cadmium toxicity than cortical bone.

For the 9-month lumbar spine data set, the simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model that provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-3). Using the constant-variance Hill model, the BMD_{sd1} and BMDL_{sd1} are 0.11 mg/kg and 0.05 mg Cd/kg/day, respectively (Figure A-1).

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Table A-3. Model Predictions for Changes in Bone Mineral Density of the Lumbar Spine in Female Rats Exposed to Cd in Drinking Water for 9 Months

Model ^a	Variance p-value ^b	p-Value for the means ^b	AIC	BMD _{sd1} (mg Cd/kg/day)	BMDL _{sd1} (mg Cd/kg/day)
Linear ^c	0.36	0.00	211.92	1.93	1.42
Polynomial (1-degree) ^c	0.36	0.00	211.92	1.93	1.42
Polynomial (2-degree) ^c	0.36	0.00	211.92	1.93	1.42
Polynomial (3-degree) ^c	0.36	0.00	211.92	1.93	1.42
Power	0.36	0.00	211.92	1.93	1.42
Hill	0.36	0.60	197.21	0.11	0.05

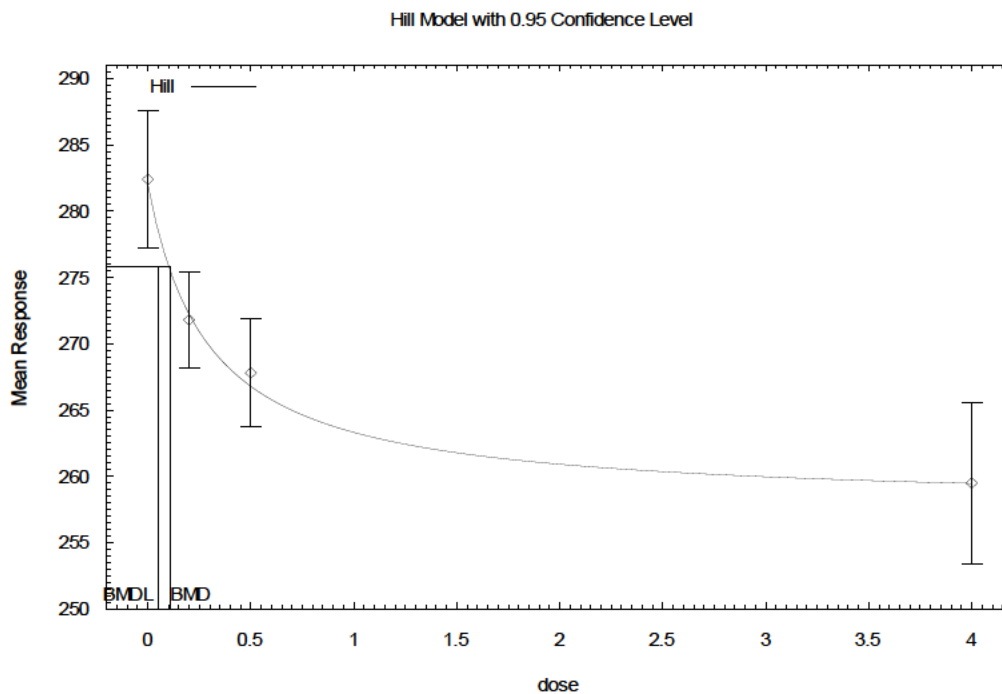
^aConstant variance assumed for all models.

^bValues <0.1 fail to meet conventional goodness-of-fit criteria.

^cRestriction = non-positive.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test; Std1 = a 1 standard deviation change from the control.

Source: Brzóska and Moniuszko-Jakoniuk 2005d

Figure A-1. Predicted and Observed Incidence of Changes in Lumbar Spine Bone Mineral Density in Female Rats Exposed to Cadmium in Drinking Water for 9 Months (Brzóska and Moniuszko-Jakoniuk 2005d)*

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*BMDs and BMDLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg Cd/kg/day.

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Uncertainty Factors used in MRL derivation:

- [] 10 for use of a LOAEL
- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Investigators estimated doses based on body weight and water consumption.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure. Numerous animal studies have examined the systemic, immunological, neurological, reproductive, and developmental toxicity of cadmium. The most sensitive systemic effect following intermediate-duration oral exposure to cadmium appears to be damage to growing bone. Exposure to 0.2 mg Cd/kg/day as cadmium chloride in drinking water for 3–12 months resulted decreases in bone mineral density, impaired mechanical strength of the lumbar spine, tibia, and femur bones, increased bone turnover, and increased incidence of deformed or fractured lumbar spine bone in young female rats (3 weeks of age at study initiation) (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c, 2010); similar findings were observed in young male rats exposed to 0.5 mg Cd/kg/day for up to 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Decreases in bone strength were also observed in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi et al. 1989); however, no skeletal effects were observed in adult or elderly female rats exposed to doses >20 mg Cd/kg/day for 4 weeks (Ogoshi et al. 1989).

Renal effects have been observed at higher doses than the skeletal effects. Vesiculation of the proximal tubules was observed in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks (Gatta et al. 1989). At approximately 3–8 mg Cd/kg/day, proteinuria, tubular necrosis, and decreased renal clearance were observed in rats (Cha 1987; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a). Liver necrosis and anemia (Cha 1987; Groten et al. 1990; Kawamura et al. 1978) were observed at similar cadmium doses.

A number of developmental effects have been observed in the offspring of rats exposed to cadmium during gestation and lactation. Decreases in glomerular filtration rates and increases in urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium were observed in 60-day-old offspring of rats administered via gavage 0.5 mg Cd/kg/day on gestation days 1–21 (Jacquillet et al. 2007). Neurodevelopmental alterations have also been observed at the low maternal doses. Delays in the development of sensory motor coordination reflexes and increased motor activity were observed at 0.706 mg Cd/kg/day (gestation days 1–21) (Ali et al. 1986), decreased motor activity at 0.04 mg Cd/kg/day (5–8 weeks of pre-gestation exposure, gestation days 1–21) (Baranski et al. 1983), decreased ambulation and rearing activity and altered ECG at 14 mg Cd/kg/day (gestation days 5–15, lactation days 2–28, postnatal days 1–56) (Desi et al. 1998) or 7 mg Cd/kg/day (F₂ and F₃ generations) (Nagymajtenyi et al. 1997) have been observed. Decreases in pup body weight were observed at ≥5 mg Cd/kg/day (Baranski 1987; Gupta et al. 1993; Kostial et al. 1993; Pond and Walker 1975) and decreases in fetal body weight or birth weight were observed at ≥2.4 mg Cd/kg/day (Petering et al. 1979; Sorell and Graziano 1990; Webster 1978; Sutou et al. 1980). Another commonly reported developmental effect was alterations in hematocrit levels or anemia in the offspring of animals exposed to ≥1.5 mg Cd/kg/day

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(Kelman et al. 1978; Baranski 1987; Webster 1978). Increases in the occurrence of malformations or anomalies is limited to a study by Sutou et al. (1980), which reported a significant delay in ossification in rats exposed to 10 mg Cd/kg/day.

The animal studies identify several sensitive targets of toxicity following intermediate-duration exposure to cadmium; these include skeletal mineralization in young female rats exposed for at least 3 months to 0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c), decreased glomerular filtration in young rats exposed during gestation to maternal doses of 0.5 mg Cd/kg/day (Jacquillet et al. 2007), and neurodevelopmental effects following gestational exposure to 0.04 mg Cd/kg/day (Baranski et al. 1983). Although the Baranski et al. (1983) study reported the lowest LOAEL, it was not selected as the principal study for derivation of an intermediate-duration MRL. For locomotor activity, a significant decrease in activity was observed in female offspring exposed to 0.04, 0.4, and 4 mg Cd/kg/day, as compared to controls; however, no significant differences were found between the cadmium groups despite the 100-fold difference in doses. Locomotor activity was also decreased in males exposed to 0.4 or 4 mg Cd/kg/day. For the rotorod test, a significant decrease in the length of time the rat stayed on the rotorod was observed in males exposed to 0.04 and 0.4 mg Cd/kg/day, but not to 4 mg Cd/kg/day and in females exposed to 0.4 and 4 mg Cd/kg/day; no differences between the cadmium groups were observed in the males and females. The results were poorly reported and the investigators did not explain the lack of dose-response of the effects or the discrepancy between genders.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cadmium
CAS Numbers: 7440-43-9
Date: September, 2012
Profile Status: Post-Public Comment Draft 2
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Graph Key: 106
Species: Human

Minimal Risk Level: 0.1 ☒ $\mu\text{g Cd/kg/day}$ ☐ $\mu\text{g Cd/m}^3$

Reference: Buchet JP, Lauwerys R, Roels H, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699-702.

Järup L, Hellstrom L, Alfven T, et al. 2000. Low level exposure to cadmium and early kidney damage: The OSCAR study. Occup Environ Med 57(10):668-672.

Suwazono Y, Sand S, Vahter M, et al. 2006. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 114:1072-1076.

Experimental design: ATSDR conducted a meta-analysis of select environmental exposure dose-response studies examining the relationship between urinary cadmium and the prevalence of elevated levels of biomarkers of renal function (Buchet et al. 1990; Järup et al. 2000; Jin et al. 2004c; Kobayashi et al. 2006; Shimizu et al. 2006; Suwazono et al. 2006; Wu et al. 2001). The studies were selected based on the following qualitative criteria: (1) the study measured an urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of low molecular weight (LMW) proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. No attempt was made to weight selected studies for quality, statistical power, or statistical uncertainty in dose-response parameters. Studies using a cut-off value for β_2 -microglobulin of $\geq 1,000 \mu\text{g/g creatinine}$ were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β_2 -microglobulin levels of 1,000–10,000 $\mu\text{g/g creatinine}$ were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in glomerular filtration rate. Additionally, an attempt was made to avoid using multiple analyses of the same study population.

The individual dose-response functions from each study were implemented to arrive at estimates of the internal dose (urinary cadmium expressed as $\mu\text{g/g creatinine}$) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). Estimates were derived from the seven environmental exposure studies listed above. When available, male and female data were treated separately; thus, 11 dose-response relationships were analyzed. For studies that did not report the UCD_{10} , the value was estimated by iteration of the reported dose response relationship for varying values of urinary cadmium, until an excess risk of 10% was achieved. For studies that reported the dose-response relationship graphically, but did not report the actual dose-response function, a function was derived by least squares fitting based on data from a digitization of the graphic

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Dose and end point used for MRL derivation: Aggregate UCD₁₀ estimates and the estimates stratified by location (i.e., Europe, Japan, China) are presented in Table A-4. The lowest UCD₁₀ (1.34 µg/g creatinine) was estimated from the European database; and the 95% lower confidence limit on this UCD₁₀ (UCDL₁₀) of 0.5 µg/g creatinine was considered as the point of departure for the MRL.

Table A-4. Estimates of the UCD₁₀ and Cadmium Intake from Environmental Exposure Dose-Response Studies

	UCD ₁₀ ^a (µg Cd/g creatinine)	Cadmium intake ^b (µg/kg/day)	
		Females	Males
Europe (n=4) ^c			
Mean	1.34	0.97	2.24
Median	—	—	—
95% CI	0.50, 2.18	0.33, 1.75	0.70, 3.94
Japan (n=4) ^d			
Mean	5.23	4.59	10.1
Median	—	—	—
95% CI	4.24, 6.21	3.67, 5.49	8.07, 12.0
China (n=3) ^e			
Mean	9.55	8.60	18.8
Median	—	—	—
95% CI	2.96, 16.1	2.48, 14.7	5.51, 31.9
All (n=11)			
Mean	4.99	4.37	9.58
Median	4.20	3.63	7.99
95% CI	1.44, 6.60	1.06, 5.86	2.45, 12.8

^aEstimates of urinary cadmium level corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (UCD₁₀).

^bUCD was transformed into estimates of chronic cadmium intake that would result in the UCD at age 55 using a modification (Choudhury et al. 2001; Diamond et al. 2003) of the Kjellström and Nordberg (1978) model.

^cDose-response function data from Buchet et al. (1990), Suwazono et al. (2006), and Järup et al. (2000); dose response data from males and females in the Buchet et al. (1990) study were treated separately.

^dDose-response function data from Kobayashi et al. (2006) and Shimizu et al. (2006); dose response data from males and females were treated separately.

^eDose-response function data from Jin et al. (2004c) and Wu et al. (2001); dose response data from males and females in the Jin et al. (2004c) study were treated separately.

UCD = urinary cadmium dose

[] NOAEL [] LOAEL [X] UCDL₁₀

The UCDL₁₀ of 0.5 µg/g creatinine was transformed into estimates of chronic cadmium intake (expressed as µg/kg/day) that would result in the UCDL₁₀ at age 55 (approximate age of peak cadmium concentration in the renal cortex associated with a constant chronic intake). The dose transformations were achieved by simulation using a modification of the Kjellström and Nordberg (1978) model. The following modifications (Choudhury et al. 2001; Diamond et al. 2003) were made to the model: (1) the equations describing intercompartmental transfers of cadmium were implemented as differential equations in Advanced Computer Simulation Language (acslXtreme, version 2.4.0.9); (2) growth algorithms for males

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and females and corresponding organ weights (O'Flaherty 1993) were used to calculate age-specific cadmium concentrations from tissue cadmium masses; (3) the cadmium concentration in renal cortex (RC, µg/g) was calculated as follows:

$$RC = 1.5 \cdot \frac{K}{KW}$$

where K is the age-specific renal cadmium burden (µg) and KW is the age-specific kidney wet weight (g) (Friberg et al. 1974)

(4) the rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur}; and (5) absorption of ingested cadmium was assumed to be 5% in males and 10% in females. The rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was estimated from the relationship between LBM (kg) and Cr_{ur}:

$$LBM = 27.2 \cdot Cr_{ur} + 8.58$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976). Lean body mass was estimated as follows (ICRP 1981):

$$LBM = BW \cdot 0.85, \text{adult females}$$

$$LBM = BW \cdot 0.88, \text{adult males}$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively.

Dose units expressed as cadmium intake (µg/kg/day), urinary cadmium excretion (µg/g creatinine), or kidney tissue cadmium (µg/g cortex) were interconverted by iterative pharmacokinetic model simulations of constant intakes for the life-time to age 55 years, the age at which renal cortex cadmium concentrations are predicted to reach their peak when the rate of intake (µg/kg/day) is constant.

The dietary cadmium intakes which would result in urinary cadmium levels of 1.34 and 0.5 µg/g creatinine (UCD₁₀ and UCDL₁₀) are 0.97 and 0.33 µg/kg/day in females and 2.24 and 0.70 µg/kg/day in males.

Uncertainty Factors used in MRL derivation:

- ☐ 10 for use of a LOAEL
- ☐ 10 for extrapolation from animals to humans
- ☒ 3 for human variability

The UCD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations; however, there is concern that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990) and diabetics were excluded from a number of human studies, and thus, an uncertainty factor of 3 was used.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

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If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The results of numerous studies of environmentally exposed populations provide strong evidence that the kidney, and possibly bone, is the most sensitive target of toxicity following chronic exposure to cadmium. Most of the studies have focused on subclinical alterations of kidney function, as measured by the urinary excretion of several biomarkers including low molecular weight proteins (β 2-microglobulin, pHc, retinol binding protein), intracellular tubular enzymes (NAG), amino acids, high molecular weight proteins (albumin), and electrolytes (potassium, sodium, calcium). Significant associations between urinary cadmium levels and an increased prevalence of abnormal levels of these biomarkers have been found in populations living in areas with moderate or high cadmium pollution or low cadmium pollution (Bandara et al. 2010; Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Ferraro et al. 2010; Hayano et al. 1996; Honda et al. 2010; Horiguchi et al. 2004, 2010; Hwangbo et al. 2011; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a, 2009b; Monzawa et al. 1998; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). Increases in the prevalence of abnormal biomarker levels appear to be the most sensitive indicator of cadmium toxicity and alterations have been observed at urinary cadmium levels ranging from 1 μ g/g creatinine (Järup et al. 2000) to 9.51 μ g/g creatinine (Jin et al. 2004a).

Several studies have examined the possible association between exposure to cadmium and bone effects. Significant associations between urinary cadmium levels and an increased risk of bone fractures at urinary cadmium levels of ≥ 0.7 μ g/g creatinine (Alfvén et al. 2004; Staessen et al. 1999; Wang et al. 2003), increased risk of osteoporosis at urinary cadmium levels of ≥ 1.5 μ g/g creatinine (Alfvén et al. 2000; Jin et al. 2004b; Wang et al. 2003), and decreased bone mineral density at urinary cadmium levels of ≥ 0.6 μ g/g creatinine (Engström et al. 2009; Nordberg et al. 2002; Schutte et al. 2008; Trzcinka-Ochocka et al. 2010).

The adverse effect levels for renal effects were similar to those observed for skeletal effects. Because the renal effects database is stronger, it was used for derivation of a chronic-duration oral MRL for cadmium. Three approaches were considered for derivation of the MRL: (1) NOAEL/LOAEL approach using a single environmental exposure study finding an increased prevalence of abnormal renal effect biomarker levels, (2) selection of a point of departure from a published benchmark dose analysis, or (3) selection of a point of departure on an analysis of the dose-response functions from a number of environmental exposure studies.

In the first approach, all studies in which individual internal doses for subjects were estimated based on urinary cadmium were considered. The Järup et al. (2000) study identified the lowest adverse effect level; the investigators estimated that a urinary cadmium level of 1 μ g/g creatinine would be associated with a 10% increase in the prevalence of abnormal pHc levels above background prevalence (approximately a 10% added risk). The European Chemicals Bureau (2007) recalculated the probability of HC proteinuria because the reference population and the study population were not matched for age (40 versus 53 years, respectively). They estimated that the probability of HC proteinuria (13%) would be twice as high as the reference population at a urinary cadmium concentration of 0.5 μ g/g creatinine. For the second approach, eight published benchmark dose analyses were evaluated (Jin et al. 2004b; Kobayashi et al. 2006, 2008a; Shimizu et al. 2006; Suwazono et al. 2006, 2011b, 2011c; Uno et al. 2005). The lower 95% confidence interval of the benchmark dose (BMDL) for low molecular weight proteinuria

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ranged from 0.7 µg/g creatinine (Uno et al. 2005) to 9.9 µg/g creatinine (Kobayashi et al. 2006). The third approach involved a meta-analysis of selected environmental exposure dose-response studies. Using individual dose-response functions from each study, estimates of the internal cadmium dose corresponding to probabilities of 10% excess risk of low molecular weight proteinuria were calculated. The lowest UCD₁₀ (1.34 µg/g creatinine) was estimated from the European database; and the 95% lower confidence limit on this UCD₁₀ (UCDL₁₀) of 0.5 µg/g creatinine was considered as a potential point of departure for the MRL.

The points of departure selected using the three different approaches are similar: 0.5 µg/g creatinine from the Järup et al. (2000) study (using the European Chemicals Bureau 2007 recalculation), 0.7 µg/g creatinine from the Uno et al. (2005) benchmark dose analysis, and 0.5 µg/g creatinine from the dose-response analysis. The third approach was selected for the derivation of the MRL because it uses the whole dose-response curves from several studies rather than data from a single study.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND**See Sample LSE Table 3-1 (page B-6)**

- (1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See Sample Figure 3-1 (page B-7)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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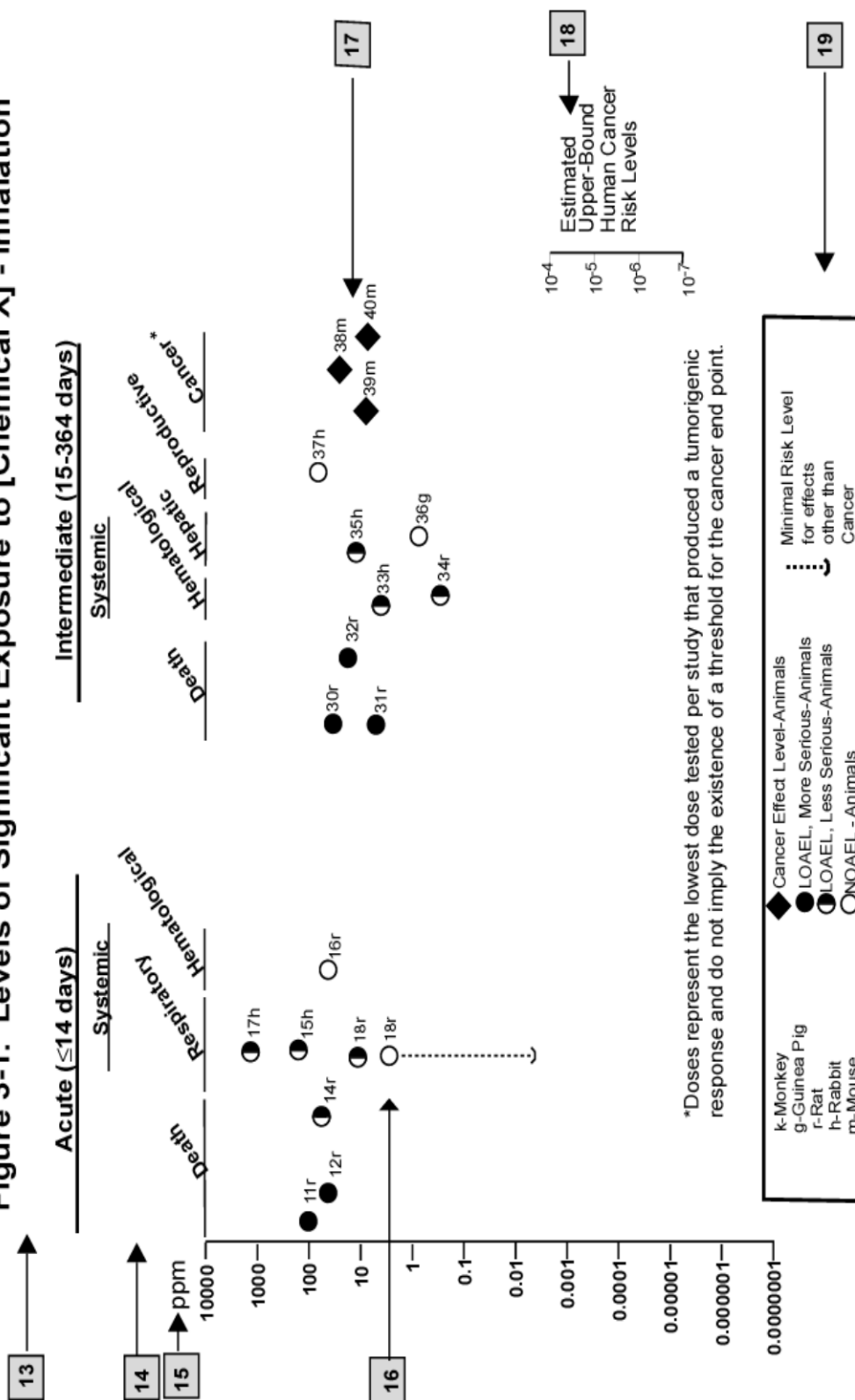
- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

CADMIUM

APPENDIX B

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD _x	dose that produces a X% change in response rate of an adverse effect
BMDL _x	95% lower confidence limit on the BMD _x
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

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DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
NA/IMDG	North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie

APPENDIX C

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

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OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD ₅₀	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

APPENDIX C

$>$	greater than
\geq	greater than or equal to
$=$	equal to
$<$	less than
\leq	less than or equal to
$\%$	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
$-$	negative
$+$	positive
$(+)$	weakly positive result
$(-)$	weakly negative result

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TOXICOLOGICAL PROFILE FOR CHROMIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2012

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for Chromium, Draft for Public Comment was released in September 2008. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the toxic substances each profile describes. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The profiles focus on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. A health effects summary describes the adequacy of information to determine a substance's health effects. ATSDR identifies data needs that are significant to protection of public health.

Each profile:

- (A) Examines, summarizes, and interprets available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) Determines whether adequate information on the health effects of each substance is available or being developed to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identifies toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are federal, state, and local health professionals; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other federal scientists also have reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Christopher J. Portier, Ph.D.
Assistant Administrator

Agency for Toxic Substances and Disease Registry

***Legislative Background**

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 **How Can (Chemical X) Affect Children?**

Section 1.7 **How Can Families Reduce the Risk of Exposure to (Chemical X)?**

Section 3.7 **Children's Susceptibility**

Section 6.6 **Exposures of Children**

Other Sections of Interest:

Section 3.8 **Biomarkers of Exposure and Effect**

Section 3.11 **Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) **Fax:** (770) 488-4178

E-mail: cdcinfo@cdc.gov

Internet: <http://www.atsdr.cdc.gov>

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Environmental Toxicology Branch (proposed) reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for chromium. The panel consisted of the following members:

1. Dr. Detmar Beyersmann, Professor Emeritus of Biochemistry, University of Bremen, Germany,
2. John Pierce Wise, Sr., Ph.D., Director, Maine Center for Toxicology and Environmental Health, Professor of Toxicology and Molecular Epidemiology, Department of Applied Medical Sciences, University of Southern Maine, 96 Falmouth St., Portland, ME 04104-9300, and
3. Richard Sedman, Ph.D., Toxicologist, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA.

These experts collectively have knowledge of chromium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chromium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Chromium has been found in at least 1,127 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which chromium is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to chromium, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), the form (chromium VI as opposed to chromium III), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS CHROMIUM?

Description	<p>Chromium is a naturally-occurring element found in rocks, animals, plants, and soil, where it exists in combination with other elements to form various compounds.</p> <p>The three main forms of chromium are:</p> <ul style="list-style-type: none">• chromium(0),• chromium(III), and• chromium(VI). <p>Small amounts of chromium(III) are needed for human health.</p>
Uses <ul style="list-style-type: none">• manufacturing	<p>Chromium is widely used in manufacturing processes to make various metal alloys such as stainless steel.</p>
Consumer products	<p>Chromium can be found in many consumer products such as:</p> <ul style="list-style-type: none">• wood treated with copper dichromate,• leather tanned with chromic sulfate, and• stainless steel cookware.• metal-on-metal hip replacements

1.2 WHAT HAPPENS TO CHROMIUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	<p>Chromium can be found in air, soil, and water after release from industries that use chromium, such as industries involved in electroplating, leather tanning, textile production, and the manufacture of chromium-based products. Chromium can also be released into the environment from the burning of natural gas, oil, or coal.</p>
Break down <ul style="list-style-type: none">• air• water and soil	<p>Chromium does not usually remain in the atmosphere, but is deposited into the soil and water.</p> <p>Chromium can change from one form to another in water and soil, depending on the conditions present.</p>

1. PUBLIC HEALTH STATEMENT

1.3 HOW MIGHT I BE EXPOSED TO CHROMIUM?

Air exposure	<p>You can be exposed to trace levels of chromium by breathing air containing it. Releases of chromium into the air can occur from:</p> <ul style="list-style-type: none">• industries using or manufacturing chromium• living near a hazardous waste facility that contains chromium• cigarette smoke <p>Rural or suburban air generally contains lower concentrations of chromium than urban air.</p> <ul style="list-style-type: none">• <10 ng/m³ in rural areas• 0–30 ng/m³ in urban areas• as a result of smoking, indoor air contaminated with chromium can be 10–400 times greater than outdoor air concentrations
Workplace air	<p>A large number of workers are potentially exposed to chromium. The highest potential exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations.</p>
Water and soil	<p>Chromium is occasionally detected in groundwater, drinking water, or soil samples. Some ways to be exposed to chromium include:</p> <ul style="list-style-type: none">• drinking water containing chromium• bathing in water containing chromium
Food	<p>The general population is most likely to be exposed to trace levels of chromium in the food that is eaten. Low levels of chromium(III) occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats.</p>

1.4 HOW CAN CHROMIUM ENTER AND LEAVE MY BODY?

Enter your body <ul style="list-style-type: none">• inhalation	<p>When you breathe air containing chromium, some of the chromium will enter your body through your lungs. Some forms of chromium can remain in the lungs for several years or longer.</p>
<ul style="list-style-type: none">• ingestion	<p>A small percentage of ingested chromium will enter the body through the digestive tract.</p>
<ul style="list-style-type: none">• dermal contact	<p>When your skin comes in contact with chromium, small amounts of chromium will enter your body.</p>
Leave your body	<p>Chromium(VI) is changed to chromium(III) in the body. Most of the chromium leaves the body in the urine within a week, although some may remain in cells for several years or longer.</p>

1. PUBLIC HEALTH STATEMENT

1.5 HOW CAN CHROMIUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Respiratory tract	<p>The most common health problem in workers exposed to chromium involves the respiratory tract. These health effects include irritation of the lining of the nose, runny nose, and breathing problems (asthma, cough, shortness of breath, wheezing). Workers have also developed allergies to chromium compounds, which can cause breathing difficulties and skin rashes.</p> <p>The concentrations of chromium in air that can cause these effects may be different for different types of chromium compounds, with effects occurring at much lower concentrations for chromium(VI) compared to chromium(III). However, the concentrations causing respiratory problems in workers are at least 60 times higher than levels normally found in the environment.</p> <p>Respiratory tract problems similar to those observed in workers have been seen in animals exposed to chromium in air.</p>
Stomach and small Intestine	<p>The main health problems seen in animals following ingestion of chromium(VI) compounds are to the stomach and small intestine (irritation and ulcer) and the blood (anemia). Chromium(III) compounds are much less toxic and do not appear to cause these problems.</p>
Male reproductive system	<p>Sperm damage and damage to the male reproductive system have also been seen in laboratory animals exposed to chromium(VI).</p>
Cancer	<p>The International Agency for Research on Cancer (IARC) has determined that chromium(VI) compounds are carcinogenic to humans. The National Toxicology Program 11th Report on Carcinogens classifies chromium(VI) compounds as known to be human carcinogens.</p> <p>In workers, inhalation of chromium(VI) has been shown to cause lung cancer. Mixed results have been found in studies of populations living in areas with high levels of chromium(VI) in the drinking water.</p> <p>In laboratory animals, chromium(VI) compounds have been shown to cause tumors to the stomach, intestinal tract, and lung.</p>

1. PUBLIC HEALTH STATEMENT

1.6 HOW CAN CHROMIUM AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	There are no studies that have looked at the effects of chromium exposure on children. It is likely that children would have the same health effects as adults. We do not know whether children would be more sensitive than adults to the effects of chromium.
Developmental effects	<p>There are no studies showing that chromium causes birth defects in humans.</p> <p>In animals, some studies show that exposure to high doses during pregnancy may cause miscarriage, low birth weight, and some changes in development of the skeleton and reproductive system. Developmental effects in animals may be related, in part, to chromium toxicity in the mothers.</p>

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHROMIUM?

Avoid tobacco smoke	Chromium is a component of tobacco smoke. Avoid smoking in enclosed spaces like inside the home or car in order to limit exposure to children and other family members.
Avoid older pressure treated lumber	In the past, pressure treated wood used chromated copper arsenate; however, the use of this product in residential settings was discontinued effective December 31, 2003. Avoiding older pressure treated lumber can reduce your risk of exposure to chromium. You may also have your water tested to ensure that you are not exposed to high levels of chromium.
Launder clothing from work sites	Clothing or items removed from the workplace may contain chromium if you are employed in a setting where occupational exposure is significant. Therefore, common sense hygiene and laundry practices may help avoid unnecessary exposures.

If your doctor finds that you have been exposed to significant amounts of chromium, ask whether your children might also be exposed. Your doctor might need to ask you state health department to investigate.

1. PUBLIC HEALTH STATEMENT

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHROMIUM?

Detecting exposure	Since chromium is a required nutrient in the body and is normally present in food, chromium is normally present in blood, urine, and body tissues.
Measuring exposure	Higher than normal levels of chromium in blood or urine may indicate that a person has been exposed to chromium. However, increases in blood and urine chromium levels cannot be used to predict the kind of health effects that might develop from that exposure.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for chromium include the following:

1. PUBLIC HEALTH STATEMENT

Levels in drinking water set by EPA	The EPA has established a maximum contaminant level of 0.1 mg/L for total chromium in drinking water. EPA currently seeks voluntary monitoring of hexavalent chromium in drinking water by municipalities. However, it is reviewing health effects data of hexavalent chromium and may set limits on its levels in drinking water in the future.
Levels in bottled water set by FDA	The FDA has determined that the chromium concentration in bottled drinking water should not exceed 0.1 mg/L.
Levels in workplace air set by OSHA	OSHA set a legal limit for chromium(VI) of 0.005 mg/m ³ chromium in air averaged over an 8-hour work day, for chromium(III) of 0.5 mg/m ³ chromium in air averaged over an 8-hour work day, and for chromium(0) of 1.0 mg/m ³ chromium in air averaged over an 8-hour work day.
Levels in workplace air set by NIOSH	NIOSH recommends an exposure limit of 0.5 mg/m ³ chromium as chromium metal and chromium(II) and chromium(III) compounds in air averaged over an 8-hour work day. NIOSH also recommends an exposure limit of 0.001 mg/m ³ for chromium(VI) compounds in air averaged over 10-hour work day.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

1. PUBLIC HEALTH STATEMENT

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: <http://www.ntis.gov/>

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHROMIUM IN THE UNITED STATES

Chromium is a naturally occurring element present in the earth's crust. Chromium is released to the environment from natural and anthropogenic sources, with the largest release occurring from industrial releases. The industries with the largest contribution to chromium release include metal processing, tannery facilities, chromate production, stainless steel welding, and ferrochrome and chrome pigment production. The estimated atmospheric concentrations of chromium in U.S. urban and nonurban areas typically contains mean total chromium concentrations ranging from 5 to 525 ng/m³. The levels of chromium in U.S. fresh waters typically range from <1 to 30 µg/L, with a median value of 10 µg/L. Typical U.S. drinking water supplies contain total chromium levels within a range of 0.2–35 µg/L however, most supplies in the United States contain <5 µg/L of chromium. Recent monitoring data of drinking water supplies in California indicated that 86% of the sources tested had levels of chromium (reported for chromium(VI)) below 10 µg/L. U.S. soil levels of total chromium range from 1 to 2,000 mg/kg, with a mean level of 37 mg/kg. In ocean water, the mean chromium concentration is 0.3 µg/L.

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products or soils that contain chromium. The primary route of nonoccupational workers, however, is food ingestion. Chromium content in foods varies greatly and depends on the processing and preparation. In general, most fresh foods typically contain chromium levels ranging from <10 to 1,300 µg/kg. Present-day workers in chromium-related industries can be exposed to chromium concentrations 2 orders of magnitude higher than the general population.

2.2 SUMMARY OF HEALTH EFFECTS

Chromium as an Essential Nutrient. Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM) of the National Research Council (NRC) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults. IOM reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–0.16 µg/L) and an average urinary chromium excretion of 0.22 µg/L or 0.2 µg/day. Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also

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referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate. The function of chromodulin, an oligopeptide complex containing four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven.

Although the Institute of Medicine considers chromium(III) an essential element, some critics question its essentiality. Reports of chromium(III) deficiency are rare and there is no recognized disease that is attributed to chromium deficiency as there is with most other essential minerals (e.g., osteoporosis associated with calcium deficiency). Evidence of overt signs of apparent chromium deficiency in humans is limited to a few case reports. In one such case report, a woman receiving total parenteral nutrition for 3 years exhibited peripheral neuropathy, weight loss, and impaired glucose metabolism. Administration of insulin did not improve glucose tolerance. Administration of 250 µg/day chromium without exogenous insulin resulted in normal glucose tolerance of an oral load of glucose and the absence of peripheral neuropathy. Thus, direct evidence of chromium(III) deficiency in humans is lacking. In animals, severe chromium deficiency is also difficult to induce, but when it was induced hyperglycemia, decreased weight gain, elevated serum cholesterol levels, aortic plaques, corneal opacities, impaired fertility, and lethality were observed. Administration of inorganic trivalent chromium compounds or extracts of brewers' yeast resulted in decreased blood glucose levels and cholesterol levels and regression of atherosclerotic plaques. Improved insulin sensitivity also resulted in an increased incorporation of amino acids into proteins and cell transport of amino acid in rats receiving supplemental chromium. Thus, whether chromium is a true essential element or a pharmacological agent is still under debate.

Studies have shown that chromium supplementation (Brewer's yeast, extracts of brewer's yeast, synthetic chromium compounds with biological activity, chromium(III) picolinate, and inorganic trivalent chromium) in deficient and marginally deficient subjects can result in improved glucose, protein, and lipid metabolism. In general, these studies have demonstrated improved glucose tolerance to an oral glucose load in Type II diabetics (adult onset) and nondiabetic elderly subjects receiving a 4–200 µg/day chromium supplement and improved plasma lipid profiles (e.g., decreased total cholesterol, LDL-cholesterol, and serum lipids and increased in HDL-cholesterol); improvements in serum lipids and cholesterol levels may be secondary to the decreased serum glucose levels.

Chromium picolinate has been used as a dietary supplement to aid in weight loss and increase lean body mass; however, the role of chromium in the regulation of lean body mass, percentage body fat, and weight reduction is highly controversial with negative and positive results being reported in the literature.

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Numerous studies have evaluated the relationship between weight loss or increases in lean body mass in active and sedentary adults and chromium picolinate supplementation, with mixed results reported. Information on adverse health effects of chromium(III) compounds, including dietary supplements, in humans and animals is reviewed below. However, based on a limited number case studies reporting adverse effects in humans ingesting high-dose chromium(III) supplements, individuals using chromium supplements are cautioned to avoid taking more than recommended doses.

Chromium Toxicokinetics. The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. For inhaled chromium compounds of any valence state, the amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g., CrCO_3), and is higher for soluble chromium(VI) compounds (e.g., $\text{K}_2\text{Cr}_2\text{O}_7$) than soluble chromium(III) (e.g., CrCl_3). Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by nutritional status. The absorption fraction is higher when dietary intakes are lower. Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged.

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics of chromium. Chromium(VI) is reduced to chromium(III) via the intermediate forms of chromium(V) and chromium(IV). Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and deoxyribonucleic acid (DNA), and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms stable complexes with hemoglobin and other intracellular proteins, which are retained for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Chromium has been shown to be secreted in bile of animals following parenteral (e.g., intravenous) injection of chromium(VI) or chromium(III) compounds. Chromium can also be eliminated by transfer to hair and nails.

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Health Effects of Chromium. The health effects associated with exposures to chromium(VI), chromium(III) and chromium (IV) are reviewed in detail in Chapter 3. In general, chromium(VI) compounds are more toxic than chromium(III) compounds. The higher toxic potency of chromium(VI) compared to chromium(III) is complex. Chromium(VI) enters cells by facilitated uptake, whereas chromium(III) crosses cell membranes by simple diffusion; thus, cellular uptake of chromium(VI) is more effective than the uptake of chromium(III). Furthermore, in biological systems, reduction of chromium(VI) to chromium(III) results in the generation of free radicals, which can form complexes with intracellular targets. Health effects of chromium compounds can vary with route of exposure, with certain effects specific for the portal of entry. For example, respiratory effects are associated with inhalation of chromium compounds, but not with oral and dermal exposures, and gastrointestinal effects are primarily associated with oral exposure. However, as described below, effects of chromium are not limited to the portal of entry, with hematological, immunological, and reproductive systems also identified as targets for chromium. In addition to noncancer health effects, results of occupational exposure studies and chronic-duration animal studies indicate that inhalation and oral exposures to chromium(VI) compounds are associated with respiratory and gastrointestinal system cancers, respectively (see discussion under chromium(VI) below for additional information).

Chromium(VI)

The primary effects associated with exposure to chromium(VI) compounds are respiratory, gastrointestinal, immunological, hematological, reproductive, and developmental. In addition, dermal and ocular irritation may occur from direct contact. Based on available dose-response data in humans and animals, the most sensitive noncancer effects of chromium(VI) compounds are respiratory (nasal and lung irritation, altered pulmonary function), gastrointestinal (irritation, ulceration and nonneoplastic lesions of the stomach and small intestine), hematological (microcytic, hypochromic anemia), and reproductive (effects on male reproductive organs, including decreased sperm count and histopathological change to the epididymis). As reviewed below, respiratory and gastrointestinal effects appear to be portal-of-entry effects for inhalation and oral exposure, respectively. Similarly, chromium sensitization, the major immunological effect of chromium(VI), typically presents as allergic contact dermatitis resulting from dermal exposures in sensitized individuals, although respiratory effects of sensitization (asthma) may also occur. Accidental or intentional ingestion of extremely high doses of chromium(VI) compounds by humans has resulted in severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects as part of the sequelae leading to death or in patients who survived because of medical treatment.

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Respiratory Effects. The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects have been observed in workers in the following chromium-related industries: chrome plating, chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. Intermediate- and chronic-duration exposure of workers to chromium(VI) compounds has resulted in epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumoconiosis, decreased pulmonary function, and pneumonia. In some chromium-sensitive patients, inhalation of airborne chromium(VI) compounds in the workplace has resulted in asthma. Nasal irritation and mucosal atrophy and decreases in pulmonary function have occurred at occupational exposure levels ≥ 0.002 mg chromium(VI)/m³ as chromium trioxide mist. Autopsies of humans who died from cardiopulmonary arrest after ingesting chromium(VI) compounds have revealed pleural effusion, pulmonary edema, bronchitis, and acute bronchopneumonia. Respiratory effects due to ingestion of nonlethal doses are not likely to occur. It is not certain whether skin contact with chromium compounds could result in respiratory effects.

Adverse effects on the respiratory system following inhalation exposure to chromium(VI) have also been observed in animals. Acute- and intermediate-duration exposure to moderate levels of chromium(VI) compounds generally caused mild lung irritation, accumulation of macrophages, hyperplasia, inflammation, and impaired lung function. A lowest-observed-adverse-effect level (LOAEL) of 0.025 mg chromium(VI)/m³ as potassium dichromate particles for increased percentage of lymphocytes in bronchoalveolar lavage (BAL) fluid in rats exposed for 28 or 90 days was identified. Obstructive respiratory dyspnea at ≥ 0.2 mg chromium(VI)/m³, fibrosis at ≥ 0.1 mg chromium(VI)/m³, and hyperplasia at ≥ 0.05 mg chromium(VI)/m³ were found in the lungs of rats exposed to sodium dichromate for 30 or 90 days. The fibrosis and hyperplasia were reversible. Increases in the levels of total protein, albumin, and activity of lactate dehydrogenase and β -glucuronidase were observed in the bronchoalveolar lavage fluid. Nasal septum perforation, hyperplasia and metaplasia of the larynx, trachea, and bronchus, and emphysema developed in mice exposed to chromium trioxide mists for 1 year. Mice exposed chronically to 4.3 mg chromium(VI)/m³ as calcium chromate also had epithelial necrosis and hyperplasia of the bronchiolar walls.

Gastrointestinal Effects. Acute oral exposure of humans to lethal or near-lethal doses of chromium(VI) has produced adverse gastrointestinal effects, including abdominal pain, vomiting,

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gastrointestinal ulceration, hemorrhage and necrosis, and bloody diarrhea. Gastrointestinal effects have also been reported in association with chronic oral exposure of humans to chromium(VI). In a cross-sectional study conducted in 1965 of 155 people whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting. Epigastric pain, irritation, and ulceration have been reported in occupational studies of chrome plating and chromate production workers. Exposures in these studies included inhalation and ingestion of chromium (e.g., mucocilliary clearance of inhaled chromium particles to the gastrointestinal tract and/or ingestion secondary to hand-to-mouth activity) and outcomes may have been influenced by other factors, such as stress and diet. Gastrointestinal effects from dermal exposures or absorption of inhaled chromium(VI) are not anticipated.

Studies in animals show that the gastrointestinal system is a primary target of intermediate- and chronic-duration oral exposure to chromium(VI). Adverse effects were observed in the gastrointestinal tract of F344/N rats and B6C3F1 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with LOAEL values of 3.5 mg chromium(VI)/kg/day for duodenal histiocytic infiltration of the duodenum in male and female rats and of 3.1 mg chromium(VI)/kg/day for epithelial hyperplasia in mice. At a higher dose (20.9 mg chromium(VI)/kg/day), more severe effects (ulcer and epithelial hyperplasia and metaplasia of the glandular stomach) were observed in rats. Histopathological changes of the duodenum (epithelial hyperplasia and histiocytic cellular infiltrate) were also reported in a 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, a LOAEL values of 2.8 mg chromium(VI)/kg/day. After exposure for 2 years, histopathological changes were observed in the gastrointestinal tract of rats and mice. In male and female rats exposed to 0.77 and 2.4 chromium(VI)/kg/day, respectively, histiocytic infiltration of the duodenum was observed. In mice, duodenal epithelial hyperplasia was observed in males and females at 0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration of the duodenum was observed in males at 2.4 mg chromium(VI)/kg/day and in females at 3.1 mg chromium(VI)/kg/day.

Results of intermediate-duration inhalation studies in animals yield mixed results regarding the potential for gastrointestinal effects. Although rats exposed by inhalation to ≤ 0.2 mg chromium(VI)/m³ as sodium dichromate for ≤ 90 days did not have histopathological changes in the gastrointestinal tract, mice exposed chronically to 4.3 mg chromium(VI)/m³ were reported to have occasional small ulcerations in the stomach and intestinal mucosa; however, the potential of oral exposure via grooming behavior cannot be excluded.

Immunological Effects. Exposure to chromium(VI) compounds may lead to allergic sensitization in some individuals. Sensitization to chromium is produced through two types of hypersensitivity reactions: type I, an immediate onset, IgE-mediated immune mechanism, and type IV, a delayed, cell-mediated immune mechanism. Following an induction phase during which the individual becomes sensitized, subsequent exposures result in an allergic response, with symptoms typically presenting as dermatitis or asthma. Sensitization may occur from inhalation, oral, and/or dermal exposure. Estimates of the prevalence of chromium sensitivity in the general U.S. population range from 0.08 to 7%, depending upon the population evaluated. For dermal responses, the allergic response following direct skin contact with chromium compounds is characterized by eczema or dermatitis; typically, chromium-induced allergic contact dermatitis is isolated to areas at the site of contact, rarely occurring in areas remote from the point of contact. However, oral exposure to chromium(VI) has been shown to exacerbate dermatitis of sensitive individuals. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin. Exposure to chromium compounds in chromium-related occupations appears to be the major cause of chromium contact dermatitis. Patch testing has identified chromium-sensitized workers in the printing and lithography industry, in automobile factories where assemblers handled nuts, bolts, and screws, in wet sandpapering of primer paint where workers were exposed to zinc chromate, in the cement industry, in railroad systems and diesel locomotive repair shops where antirust diesel-engine coolants and radiator fluids contained sodium chromate, in tanneries, and in the welding, plating, wood, and paper industries. Other sources of chromium that have resulted in chromium sensitivity include dichromate-containing detergents and bleach, glues, machine oils, foundry sand, match heads, boiler linings, and magnetic tapes. Exposure to low levels of chromium as found in consumer products could result in sensitization or a reaction in sensitized individuals; therefore, in hypersensitive individuals may develop rashes and erythema from contact with consumer products containing chromium. Oral doses of potassium dichromate exacerbated the dermatitis of sensitive individuals.

Several studies have estimated the exposure level required to elicit a dermal response in chromium-sensitized individuals; exposure levels of 4–25 ppm produced sensitization and elicitation of chromium-induced allergic dermatitis. However, confounding factors, such as variability in testing methods (including different chromium compounds used in challenge testing) and individual sensitivity, complicate interpretation of results. Furthermore, the response of an individual to dermal challenge may vary over time due to changes in exposure to the sensitizing agents; if an individual is removed from

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exposure, circulating IgE levels may decrease, resulting in decreased sensitivity to dermal challenge. Therefore, it is anticipated that the exposure level required to elicit a dermal response in sensitized individuals will be highly variable.

Asthmatic attacks have occurred in chromium-sensitive individuals exposed by inhalation in occupational settings to chromium trioxide vapors and chromium fumes from stainless steel welding. When challenged with sodium chromate or potassium dichromate via nebulizer, chromium-sensitive patients displayed anaphylactoid reactions, characterized by dermatitis, facial angioedema and erythema, nasopharyngeal pruritus, cough, wheezing, bronchospasms, increased plasma histamine levels, urticaria, and decreased forced expiratory volume. While chromium-induced asthma might occur in some sensitized individuals exposed to elevated concentrations of chromium in air, the number of sensitized individuals is low, and the number of potentially confounding variables in the chromium industry is high.

Studies in animals also indicate that the immune system is a target for inhaled and ingested chromium(VI) compounds. Effects reported include stimulation of the humoral immune system and increased phagocytic activity of macrophages, increased proliferative responses of splenocytes to T- and B-cell mitogens and to the antigen mitomycin C and histopathological alteration (histiocytic cellular infiltration) of pancreatic lymph nodes; contact dermatitis has been elicited in guinea pigs and mice.

Hematological Effects. As discussed above (*Chromium Toxicokinetics*), chromium(VI) is distributed to and accumulated by the erythrocyte; once inside the cell, it is rapidly reduced to chromium(III) via the reactive intermediates chromium(V) and chromium(IV), and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is relatively stable and remains sequestered within the cell over the life-span of the erythrocyte, with approximately 1% of chromium eluting from the erythrocyte daily. Occupational studies and other studies in humans have not consistently reported hematological effects, although microcytic, hypochromic anemia has been reported in several recent animals studies on chromium(VI) compounds (detailed discussion follows). However, it is possible that small, exposure-related changes in hematological parameters may not have been detected in occupational exposure studies, if values were within normal clinical ranges. Hematological findings in humans exposed to lethal doses of chromium(VI) compounds are difficult to interpret in the context of multiple systemic effects observed leading up to death, including hemorrhage.

Results of acute-, intermediate-, and chronic-duration studies in animals identify the hematological system as one of the most sensitive effects of oral exposure to chromium(VI). Microcytic, hypochromic

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anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in rats and mice orally exposed to chromium(VI) compounds for exposure durations ranging from 4 days to 1 year. The severity of anemia exhibited dose- and duration-dependence, with maximum effects observed after approximately 3 weeks of exposure; with increasing exposures durations (e.g., 14 weeks–1 year), anemia is less severe, presumably due to compensatory hematopoietic responses. In general, effects observed in rats were more severe than those in mice.

Acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, produced a slight, but statistically significant decrease (2.1%) in MCH in rats exposed to 2.7 mg chromium(VI)/kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses (≥ 7.4 mg chromium(VI)/kg/day), additional decreases in MCH and decreased MCV were observed. Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 mg chromium(VI)/kg/day, respectively; a no-observed-adverse-effect level (NOAEL) was not established. Although the magnitude of changes to hematological parameters after acute exposure was minimal, since severe effects on hematological parameters were observed following intermediate exposure durations, with severity peaking at exposure durations of 22 days to 3 months, the minimal hematological alterations observed following acute exposure are considered to be indicative of adverse hematological effects.

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days. Decreased Hct, Hgb, MCV, and MCH occurred at ≥ 0.77 mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day. After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days. Hematological effects, including decreased hematocrit, hemoglobin, and erythrocyte count, have also been reported in rats exposed to chromium trivalent oxide mist for 90 days, with a LOAEL value of 0.23 mg chromium(VI)/m³.

Reproductive Effects. Results of studies in humans and animals suggest that chromium(VI) causes adverse reproductive effects, although evidence from studies in animals is much stronger than from studies in humans. Although information regarding reproductive effects in humans is limited, the following effects have been reported: a significant increase in the number of morphologically abnormal sperm; significant decreases on sperm count and motility; and greater incidences of complications during

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pregnancy and childbirth (toxicosis and postnatal hemorrhage). There no evidence of reproductive effects in humans environmentally exposed to chromium(VI).

Studies in laboratory animals show that acute- and intermediate-duration exposure to chromium(VI) produces adverse reproductive effects, with the male reproductive system exhibiting the highest sensitivity. Following a 6-day gavage administration of ≥ 5.2 mg chromium(VI)/kg/day as chromic acid to Wister rats, decreased sperm count, increased percentage of abnormal sperm, and morphological changes to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed (observations were made 6 weeks after completion of treatment); a NOAEL was not defined in this study. The male reproductive system was identified as a target for oral chromium(VI) exposure in intermediate-duration studies in monkeys, rats, and rabbits. Decreased sperm count and motility and histopathological changes to the epididymis (ductal obstruction, development of microcanals, depletion of germ cells, hyperplasia of Leydig cells, and Sertoli cell fibrosis) have been reported in monkeys exposed to 2.1 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 180 days. Effects on male reproductive organs and sexual behavior in rats and mice have been reported at doses of ≥ 2.6 mg chromium(VI)/kg/day.

In NTP studies designed to confirm or refute these findings of one study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated. Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects at daily doses up to 32.2 mg chromium(VI)/kg/day. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months.

Other reproductive effects reported in rats and mice include altered weights of female reproductive organs, decreased number of follicles and ova, increased pre- and/or postimplantation losses, and increased resorptions at doses of ≥ 5 mg chromium(VI)/kg/day. Mixed results have been found in studies designed to assess the effects of chromium(VI) exposure on fertility. No effects on fertility were observed in mice exposed to ≤ 37 mg chromium(VI)/kg/day as potassium dichromate in the diet. Decreased mating and fertility, increased preimplantation losses, and increased resorptions have been observed in rats and mice exposed to ≥ 37 mg chromium(VI)/kg/day or 52 mg chromium(VI)/kg/day as

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potassium dichromate in drinking water for 20 or 90 days prior to mating. Pre- and postimplantation loss and decreased litter size was also observed in mice exposed to ≥ 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water throughout gestation. Significant decreases in the number of implantations and viable fetuses were observed when male mice exposed to 6 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks were mated with unexposed female mice; however, sperm count was not measured and the classification of non-viable fetuses was not presented in this report. However, a similarly designed study did not find any alterations in the number of implantations or viable fetuses in unexposed female rats mated with males exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 12 weeks. It is not known if the species difference contributed to these conflicting results. Decreases in the number of implantations and viable fetuses and an increase in the number of animals with resorptions were also seen in females exposed for 12 weeks to 6 mg chromium(VI)/kg/day as potassium dichromate mated with unexposed males.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to chromium compounds. A number of oral exposure animal studies have shown that chromium(VI) is a developmental toxicant following premating and/or *in utero* exposure, or lactational exposure. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed at relatively high doses (e.g., ≥ 35 mg chromium(VI)/kg/day). In mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3, a decreased number of pregnancies were observed; exposure on gestational days 4–6 resulted in decreased number of viable fetuses and increased number of resorptions, but did not alter the number of pregnancies. Exposure of female rats to ≥ 37 mg chromium(VI)/kg/day and mice to ≥ 52 mg chromium(VI)/kg/day to potassium dichromate(VI) in drinking water for 20 or 90 days followed by mating to unexposed males resulted in fetal mortality (postimplantation losses, resorptions, and decreased number of live fetuses), decreased growth (decreased fetal body weights and crown-rump length), reduced ossification, subdermal hemorrhagic patches, and kinky tails. Similar effects (increased resorptions, increased postimplantation losses, subdermal hemorrhages, decreased cranial ossification, tail kinking, and decreased fetal body weight and decreased crown-rump length) were observed in the offspring of mice exposed to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation. In mice exposed to 53 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestational days 6–14, fetal mortality, subdermal hemorrhagic patches, and reduced ossification were observed in the offspring.

Impaired development of the reproductive system (delayed vaginal opening) was observed in the offspring of mice exposed to 66 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on gestation day 12 through lactation day 20. Delayed vaginal opening was also reported in offspring of rats exposed to ≥ 2.9 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on postnatal days 1–21. Perinatal exposure to doses ≥ 2.9 mg chromium(VI)/kg/day as potassium dichromate in the drinking water caused oxidative stress in the uterus, liver, kidney, and bone from the offspring. Microscopic examination of the kidney, liver, and bone showed morphological alterations in the three tissues. A single study reported that gavage administration of 4.4 mg chromium(VI)/kg/day as potassium dichromate to neonatal rats reduced mandibular growth and delayed tooth eruption.

Dermal Effects. Chromium(VI) compounds can produce effects on the skin and mucous membranes. These include irritation, burns, ulcers, and an allergic type of dermatitis. Irritation of respiratory mucosal tissues, nasal septum ulcers, and perforation are reviewed above under Respiratory Effects and allergic dermatitis is reviewed above under Respiratory Effects and Immunological Effects. Most dermal effects reported were either due to occupational intermediate-chronic exposure or acute exposure to high levels of chromium compounds. Environmental exposure to chromium compounds is not likely to result in dermal effects. Acute dermal exposure to chromium(VI) compounds can cause skin burns. Application of a salve containing potassium chromate to the skin of some individuals to treat scabies resulted in necrosis and sloughing of the skin, and some individuals even died as a result of infections of these areas. A worker whose skin came into direct contact with the chromic acid as a result of an industrial accident developed extensive skin burns.

Although skin contact with chromate salts may cause rashes, untreated ulcers or sores (also called chrome holes) on the skin can be a major problem because they can deeply penetrate the skin with prolonged exposure. For example, in an early case of a tannery worker, the penetration extended into the joint, necessitating amputation of the finger. However, chrome sores heal if exposure is discontinued, leaving a scar. Chrome sores are more often associated with occupational exposure to chromium(VI) compounds. Although chrome sores are more likely associated with direct dermal contact with solutions of chromates, exposure of the skin to airborne fumes and mists of chromium(VI) compounds may contribute to the development. Industries that have been associated with the development of chrome sores in workers include chromate and dichromate production, chrome plating, leather tanning, planographic printing, and chromite ore processing. Among the chromium(VI) compounds that workers in these industries are exposed to are chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate.

In addition, tonsillitis, pharyngitis, atrophy of the larynx, and irritation and ulceration of mouth structures and buccal mucosa can occur from exposure to high levels of chromium(VI) compounds. These effects were seen in workers in chrome plating plants, where excessively high concentrations of chromium trioxide fumes were present. High incidences of inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontitis were also observed in chromate production workers. Oral doses of potassium dichromate exacerbated the dermatitis of chromium sensitized individuals.

Dermal effects observed in animals after direct application of potassium dichromate to their skin include inflammation, necrosis, corrosion, eschar formation, and edema in rabbits and skin ulcers in guinea pigs.

Ocular Effects. Ocular effects can occur as a result of direct contact of eyes with chromium(VI) compounds. Effects reported include corneal vesication in a man with ocular exposure to a drop or crystal of potassium dichromate and congestion of the conjunctiva, discharge, corneal scar, and burns in chromate production workers as a result of accidental splashes.

Genotoxicity. Numerous studies have evaluated the genotoxicity of chromium(VI) compounds. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Although most of the older occupational exposure studies gave negative or equivocal results, more recent studies have identified chromosomal effects in exposed workers. Findings from occupational exposure studies are supported by results of *in vivo* studies in animals, *in vitro* studies in human cell lines, mammalian cells, yeast and bacteria, and studies in cell-free systems.

Cancer. Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, and ferrochromium alloy production. Numerous studies of cancer mortality among chromate production workers have been reported. Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed. In chromate pigment and chrome plating workers,

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elevated lung cancer rates in comparison to reference populations (e.g., standard mortality ratios [SMRs]) and increased lung cancer rates in association with increased potential for chromium exposure (e.g., job type, employment duration) have been reported. Workers in the stainless steel welding and ferrochromium alloy industries are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in these populations have been mixed. Environmental exposure of humans to chromium(VI) in drinking water resulted in statistically significant increases in stomach cancer. However, a re-analysis of these data using a more relevant control group did not find a significant increase in stomach cancer. Another study reported an increased incidence of liver, lung, and kidney and urogenital organ cancers in residents living in an area of Greece with elevated chromium(VI) levels in the drinking water. Two other ecological studies have not found elevated cancer risks in populations with contaminated drinking water.

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to 4.3 mg chromium(VI)/m³ as calcium chromate had a 2.8-fold greater incidence of lung tumors, compared to controls. In addition, numerous animal studies using the intratracheal, intrapleural, and intrabronchial routes of exposure show that chromium(VI) produces respiratory tract tumors. However, no carcinogenic effects were observed in rats, rabbits, or guinea pigs exposed to 1.6 mg chromium(VI)/m³ as potassium dichromate or chromium dust 4 hours/day, 5 days/week.

Exposure of rats and mice to sodium dichromate dihydrate in drinking water for 2 years resulted in cancers of the gastrointestinal tract. In male and female rats, the incidences of neoplasms of the squamous epithelium of the oral mucosa and tongue were significantly increased in males (7.0 mg chromium(VI)/kg/day) and females (5.9 mg chromium(VI)/kg/day); in mice, the incidence of neoplastic lesions of the small intestine (duodenum, jejunum, and ileum) was increased in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. The National Toxicology Program concluded that results demonstrate clear evidence of carcinogenic activity in male and female F344/N rats (increased incidences of squamous cell neoplasms of the oral cavity) and in male and female B6C3F1 mice (increased incidences of neoplasms of the duodenum, jejunum, or ileum). Mice exposed to chromium(VI) as potassium chromate (9 mg chromium(VI)/kg/day) in drinking water for three generations (880 days) showed statistically significant increases in the incidence of forestomach adenoma or carcinomas of the forestomach and in the incidence of forestomach adenomas alone, compared to control; however, study authors concluded that evidence of carcinogenicity was equivocal.

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NTP lists certain chromium compounds as substances that are *known to be human carcinogens*. This classification is based on sufficient evidence for a number of chromium(VI) compounds (calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate). The International Agency for Research on Cancer (IARC) classified chromium(VI) as *carcinogenic to humans (Group 1)* and metallic chromium and chromium(III) compounds as *not classifiable as to their carcinogenicity to humans (Group 3)*. EPA has classified chromium(VI) as *a known human carcinogen* by the inhalation route of exposure.

Chromium(III)

Although much less information is available on the health effects of chromium(III) compounds compared to that for chromium(VI) compounds, chromium(III) compounds appear to be less toxic than chromium(VI) compounds. Health effects associated with exposure to chromium(III) compounds have been reported in studies of occupationally exposed populations and individuals; however, interpretation of study results is complicated by concomitant exposures to chromium(VI) or other compounds that can induce adverse health effects. Similarly, interpretation of findings in case reports of exposures to dietary supplements containing high-dose chromium(III) are also complicated, since most supplements contain numerous chemicals; thus, the most reliable information on adverse health effects of chromium(III) is obtained from studies in animals. Chromium(III) picolinate, a dietary supplement, has been shown to be mutagenic in bacterial and mammalian cells *in vitro*.

The primary effects of chromium(III) compounds are on the respiratory and immunological systems. As described below, respiratory effects appear to be portal-of-entry effects for inhalation exposure. Similarly, chromium allergic dermatitis, the major immunological effect of chromium(III), is typically elicited by dermal contact in sensitized individuals; however, initial sensitization may result from inhalation, oral, or dermal exposure or from a combination of these exposure routes. Conflicting results of studies in animals have been reported in developmental and reproductive studies of chromium(III) compounds; however, results provide evidence of adverse effects on the developing and adult reproductive system. Evidence of developmental or reproductive effects of chromium(III) in humans has not been identified. Based on results of chronic-duration oral studies in animals, chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) do not appear to produce gastrointestinal, hematological, hepatic, renal, cardiovascular, endocrine, or musculoskeletal effects. This is in contrast to chromium(VI) compounds which produce effects in the gastrointestinal, hematological, hepatic and renal systems.

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Respiratory Effects. Occupational exposure studies and case reports indicate that respiratory effects occur from exposure of humans to chromium(III) compounds; however, results of these studies are difficult to interpret since most study populations were also exposed to chromium(VI) compounds or other compounds associated with respiratory effects, and/or the studies were not adequately controlled for other confounding factors (e.g., respiratory diseases). Acute- and chronic-duration studies in animals indicate that the respiratory tract is the primary target of inhaled chromium(III). Analysis of BAL fluid from rats exposed for 5 days to 3–30 mg chromium(III)/m³ as basic chromium sulfate (soluble) showed alterations, including increased amounts of cell debris and lysed cells and significant decreases in nucleated cells and in the percentage of segmented neutrophils and mononuclear cells; cytoplasmic accumulation of a yellow crystalline material in mononuclear cells was observed in BAL fluid of rats exposed to 3–30 mg chromium(III)/m³ as chromic oxide (insoluble). With longer exposure (13 weeks), histopathological changes to respiratory tissues and increased lung weights were observed in rats exposed to ≥ 3 mg chromium(III)/m³ chromic oxide or basic chromium sulfate. However, differences were observed in severity and location of respiratory effects produced by insoluble chromic oxide and soluble basic chromium sulfate; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). Differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Studies examining respiratory effects from chronic-duration inhalation exposure were not identified. Respiratory effects from oral or dermal exposure to chromium(III) compounds have not been reported.

Immunological Effects. As discussed above for chromium(VI) compounds, exposure to chromium compounds may induce allergic sensitization in some individuals. In patients with known chromium-induced allergic dermatitis, positive results have been reported using patch tests with chromium(III) compounds as the challenge agent, suggesting that allergic sensitization to chromium(III) can occur. In sensitized patients, dermal responses were elicited using a concentration of 1 mg chromium(III)/L as chromium trichloride. However, since positive responses were also observed on challenge with chromium(VI) compounds, it is unclear if individuals were sensitized to both chromium(VI) and chromium(III) or if cross-sensitivity occurs between chromium(VI) and chromium(III). Studies in animals show that chromium(III) can induce sensitization and that cross-reactivity occurs between chromium(VI) and chromium(III). Sensitization to chromium(III) was observed in guinea pigs treated with a series of intradermal injections of 0.004 mg chromium(III)/kg as chromium trichloride. In guinea

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pigs sensitized with chromium(III), cross-sensitivity with chromium(VI) was observed on patch test challenge.

Reproductive Effects. Adverse reproductive effects have been observed in rats and mice exposed orally to chromium(III) compounds, although conflicting results have been reported. Adverse reproductive effects have been reported following acute- and intermediate-duration exposure of animals to chromium(III) by gavage or in drinking water; effects include decreased number of pregnancies in female rats administered 33.6 mg chromium(III)/kg/day, alterations in sexual behavior, aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day), decreased number of pregnant female Swiss mice following the mating of unexposed females to exposed males (13 mg chromium(III)/kg/day), impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males, and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day). Decreased spermatogenesis was observed in BALB/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks.

In contrast to the reproductive effects of chromium(III) chloride in drinking water, dietary exposure to chromium picolinate or chromium nicotinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages, and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice. No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or 0.22 and 0.25 mg chromium(III)/kg/day, respectively, for 1 year.

In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed), or to differences in toxicity of the specific chromium(III) compounds evaluated.

Developmental Effects. Little information is available on the potential developmental effects of chromium(III) compounds, although results of available studies are conflicting. Chromium(III) did not

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produce developmental effects in offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period. Significant decreases were observed in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males and ovaries and uterus in females) of offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20; however, fertility was not affected when these exposed offspring were mated with unexposed animals. The number of pregnancies was decreased in rats administered 33.6 mg chromium(III)/kg/day (only dose tested) by gavage as chromium chloride on gestational days 1–3, although when exposed on gestational days 4–6, no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed. In a different type of study, neurological testing of offspring of mice exposed during gestation and lactation to 25 mg chromium(III)/kg/day as chromium picolinate in the diet did not reveal significant differences, as compared to controls. Thus, the available evidence does not indicate that exposure to chromium(III) consistently produces adverse developmental effects.

Cancer. No studies evaluating the carcinogenic activity of chromium(III) compounds in humans were identified. In male rats exposed to dietary chromium picolinate for 2 years, the incidence of preputial gland adenoma was significantly increased in males at 61 mg chromium(III)/kg/day, with the incidence also exceeding the historical control ranges; however, the incidence was not increased at a higher dose (313 mg chromium(III)/kg/day) and similar lesions were not observed in corresponding tissues in female rats or in male and female mice. Therefore, one study considered the evidence of carcinogenic activity to be equivocal. The relationship of preputial gland adenoma to male reproductive function in this study was not defined.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for chromium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs—Chromium(VI)

Acute. The inhalation database for acute-duration exposure of humans to inhaled chromium(VI) compounds is limited to a few studies reporting signs of respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headaches in individuals or small numbers of workers ($n \leq 5$) exposed to high concentrations of chromium(VI) (Lieberman 1941; Meyers 1950; Novey et al. 1983). In addition, acute inhalation exposure of individuals previously sensitized to chromium compounds has produced symptoms of asthma and signs of respiratory distress consistent with a type I allergic response (decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, blocked nasal passages, cough, and wheeze) (Leroyer et al. 1998; Olaguibel and Basomba 1989); however, the available data are not adequate to characterize the exposure-response relationship for effects of acute inhalation challenge in sensitized individuals. No other effects of acute inhalation exposure of humans to chromium(VI) have been reported.

The acute toxicity of inhaled chromium(VI) in animals has not been well investigated, and most studies are 4-hour lethality studies (American Chrome and Chemicals 1989; Gad et al. 1986). Nasal hemorrhage was observed in two of five rats after inhalation for 10 days to 1.15 mg chromium(VI)/m³ during a 13-week exposure study (Kim et al. 2004), with no nasal effects observed at 0.49 mg chromium(VI)/m³. However, only a small number of animals were evaluated and histopathological evaluations of the respiratory tract (or other tissues) were not conducted following the acute-duration period; thus, data are not suitable for defining NOAEL or LOAEL values for respiratory effects. Although longer duration inhalation studies show that the respiratory tract is a sensitive target of inhaled chromium(VI), the data are insufficient to determine acute-duration exposure levels that would produce respiratory tract, or other effects. In the absence of studies that could be used to identify the targets of low level exposure, an acute-duration inhalation MRL for hexavalent chromium was not derived.

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Intermediate

- An inhalation MRL of 5×10^{-6} mg chromium(VI)/m³ has been derived for intermediate (15–364 days) exposure for dissolved hexavalent chromium aerosols and mists.

The available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects. Although the respiratory system is the most sensitive target for inhalation exposure to both types of chromium(VI) compounds, the primary respiratory effects of inhaled chromic acid mists are observed in the nose (see the following discussion), while the effects of inhaled particulate chromium(VI) compounds occur throughout the respiratory tract. Since toxic potencies of these compounds appear to be different and the likelihood for environmental exposure to chromium trioxide (e.g., chromic acid mist) and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

The intermediate-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists (Gibb et al. 2000a, 2000b; Gomes 1972; Kleinfeld and Rosso 1965; Lindberg and Hedenstierna 1983); these studies identify the upper respiratory tract as the primary target of exposure. Upper respiratory effects include nasal irritation, ulceration, and mucosal atrophy and rhinorrhea, with LOAEL values ranging from 0.002 to 0.1 mg chromium(VI)/m³. Other effects (e.g., non-respiratory) specific for dissolved chromium(VI) aerosols and mists in humans have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation.

Available animal studies on the effects of intermediate-duration exposure to dissolved chromium(VI) aerosols and mists identify the respiratory tract as the primary target, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m³ (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). Respiratory effects reported in animals exposed to chromium(VI) trioxide include alveolar inflammation in rats (Kim et al. 2004) and nasal septal perforation and symptoms of emphysema in mice (Adachi 1987; Adachi et al.

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1986). The only other effect (e.g., non-respiratory) observed in animal studies on dissolved chromium(VI) aerosols and mists were hematological effects and decreased body weight in rats exposed to chromium trioxide mist for 13 weeks. Hematological effects include decreased in hematocrit at ≥ 0.23 and $1.15 \text{ mg chromium(VI)/m}^3$ (but not $0.49 \text{ mg chromium(VI)/m}^3$) decreased hemoglobin at $\geq 0.49 \text{ mg chromium(VI)/m}^3$ and decreased erythrocyte count at $1.15 \text{ mg chromium(VI)/m}^3$ (Kim et al. 2004). In this study, body weight gain was also decreased by $\sim 9\%$, with NOAEL and LOAEL values of 0.49 and $1.15 \text{ mg chromium(VI)/m}^3$, respectively.

Based on a comparison of LOAEL values for respiratory effects, hematological effects, and decreased body weight gain, the respiratory tract was identified as the most sensitive effect of intermediate-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of $0.002 \text{ mg chromium(VI)/m}^3$ was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters observed in workers exposed to chromic acid mist (Lindberg and Hedenstierna 1983); therefore, this value was selected as the basis for derivation of the intermediate-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluated by Lindberg and Hedenstierna (1983) included 85 male and 19 female chrome plating workers exposed to chromic acid and a reference group of 119 auto mechanics not exposed to chromium. Workers were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, with a mean of 2.5 years, spanning both intermediate and chronic durations. Since the study population included workers exposed for an intermediate duration, data are considered appropriate for derivation of the intermediate-duration inhalation MRL. Nasal irritation ($p < 0.05$), mucosal atrophy ($p < 0.05$), and ulceration ($p < 0.01$), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to $\geq 0.002 \text{ mg chromium(VI)/m}^3$ as chromic acid. Approximately 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Additional details on study methods and results are provided in Appendix A.

The LOAEL of $0.002 \text{ mg chromium(VI)/m}^3$ was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ($\text{LOAEL}_{\text{ADJ}}$) of $0.0005 \text{ mg chromium(VI)/m}^3$. The intermediate-duration MRL of 5×10^{-6} was obtained by dividing the $\text{LOAEL}_{\text{ADJ}}$ ($0.0005 \text{ mg chromium(VI)/m}^3$) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

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- An inhalation MRL of 0.0003 mg chromium(VI)/m³ was derived for intermediate exposures to particulate chromium(VI) compounds.

As discussed above, available data on inhalation exposure of humans and animals to chromium(VI) compounds indicate that dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds have different toxic potencies for producing adverse respiratory effects (the primary target organ). Furthermore, since the likelihood for environmental exposure to chromium trioxide and other soluble chromium(VI) compound mists is less than the likelihood for environmental exposure to particulate chromium(VI) compounds, distinct intermediate-duration inhalation MRLs have been derived for dissolved chromium(VI) compounds (aerosols and mists) and particulate chromium(VI) compounds.

Although few animal studies have reported adverse effects of intermediate-duration inhalation exposure to particulate chromium(VI) compounds (Cohen et al. 1998; Glaser et al. 1985, 1990), results of available studies conducted in rats indicate that the respiratory tract is the primary target organ. In rats exposed to inhaled sodium dichromate for 30–90 days, adverse respiratory effects included obstructive respiratory dyspnea, increased lung weights, hyperplasia of the lung, focal inflammation of the upper airway, and alterations to BAL fluid concentrations of lactate dehydrogenase, protein, and albumin, with a LOAEL value of 0.2 mg chromium(VI)/m³ (Glaser et al. 1990). Other effects reported in the Glaser et al. (1985, 1990) studies were an increased percentage of lymphocytes in BAL fluid (LOAEL of 0.025 mg chromium(VI)/m³), increased serum phospholipids and triglycerides (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m³, respectively), increased white blood cell count (LOAEL value of 0.05 mg chromium(VI)/m³), decreased body weight gain (NOAEL and LOAEL values of 0.1 and 0.2 mg chromium(VI)/m³), and an enhanced immune response to sheep erythrocytes (LOAEL 0.025 mg chromium(VI)/m³); however, the toxicological significance of these findings is uncertain. Effects that may be indicative of altered immune function (altered white blood cell counts and cytokine levels in BAL fluid) were observed in rats exposed to 0.36 mg chromium(VI)/m³ as potassium chromate or barium chromate for 2–4 weeks (Cohen et al. 1998); however, results of this study are difficult to interpret, since effects were not clearly adverse, only one exposure level was evaluated, and histopathological assessment of respiratory tissues (or other tissues) was not conducted.

Based on the available data, respiratory effects were identified as the most sensitive target of intermediate-duration exposure to particulate chromium(VI) compounds, with the study by Glaser et al. (1990) selected as the critical study. In this study, 8-week-old male Wistar rats (30 animals/group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m³ as sodium

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dichromate aerosol particulates. Detailed discussion of study methods is presented in Appendix A. No deaths or abnormal clinical signs occurred at any of the exposures. Obstructive respiratory dyspnea occurred at ≥ 0.2 mg chromium(VI)/m³ after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at 0.05 mg chromium(VI)/m³ for 30 days, and at 0.1 mg chromium(VI)/m³ for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at 0.05 mg chromium(VI)/m³ at 30 days. Lung fibrosis occurred at 0.1 mg chromium(VI)/m³ for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase and β -glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m³ for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. Additional details on study results are presented in Appendix A.

Results of the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) were identified as the basis for derivation of an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs (defined as the 95% lower limit on the concentration corresponding to a 10% relative change in the end point compared to the control) for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day). Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs. The lowest BMCL, 0.016 mg chromium(VI)/m³ for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m³ was converted to a human equivalent concentration (BMCL_{HEC}) of 0.010 mg chromium(VI)/m³ using the regional deposited dose ratio (RDDR) program (EPA 1994c) (see Appendix A for details).

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The intermediate-duration inhalation MRL of 0.0003 mg chromium(VI)/m³ for hexavalent chromium particulate compounds was derived by dividing the BMCL_{HEC} of 0.010 mg chromium(VI)/m³ by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Chronic

- An inhalation MRL of 5×10^{-6} mg chromium(VI)/m³ has been derived for chronic (≥ 365 days) exposure for dissolved hexavalent chromium aerosols and mists.

The chronic-duration inhalation database for humans exposed to dissolved chromium(VI) aerosols and mists consists of occupational exposure studies on chromium trioxide mists, reporting effects to the respiratory, renal, and gastrointestinal systems (Franchini and Mutti 1988; Gibb et al. 2000a, 2000b; Hanslian et al. 1967; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975). Respiratory effects included bleeding nasal septum, nasal mucosal atrophy, nasal septal ulceration and perforation, epistaxis, rhinorrhea, and decreased lung function, with LOAEL values ranging from 0.002 to 0.414 mg chromium(VI)/m³. Effects indicative of renal toxicity include increased retinol binding protein and tubular antigen and increased urinary β -2-microglobulin (Franchini and Mutti 1988; Lindberg and Hedenstierna 1983); LOAEL values for these effects range from 0.004 to 0.05 mg chromium(VI)/m³. Gastrointestinal effects reported in workers include stomach pains, cramps, and ulcers, with a LOAEL value of 0.004 mg chromium(VI)/m³ (Lucas and Kramkowski 1975). Other effects specific for dissolved chromium(VI) aerosols and mists in humans exposed for chronic exposure durations have not been reported. Exposure to chromium(VI) compounds (not compound-specific) can produce allergic sensitization, which may manifest as symptoms of asthma upon subsequent inhalation exposures (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989). The exposure route for the initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal exposures; however, the available data do not define the exposure-response relationship for chromium sensitization by inhalation. Studies in animals evaluating the effects of chronic-duration exposure to dissolved chromium(VI) aerosols and mists were not identified.

Based on a comparison of LOAEL values for respiratory, renal and gastrointestinal effects in workers, the respiratory tract was identified as the most sensitive effect of chronic-duration inhalation exposure to dissolved chromium(VI) aerosols and mists. The lowest LOAEL value of 0.002 mg chromium(VI)/m³ was reported for nasal irritation, mucosal atrophy, and ulceration and decreases in spirometric parameters in workers occupationally exposed to chromic acid mist (Lindberg and Hedenstierna 1983); therefore, this

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value was selected as the basis for derivation of the chronic-duration inhalation MRL for dissolved chromium(VI) aerosols and mists. The population evaluated in this study had a mean exposure duration of 2.5 years, with a range of 0.1–23.6 years, spanning both intermediate and chronic durations. A description of study methods and results is provided above under the discussion of Intermediate-Duration Inhalation MRL for Chromium(VI) aerosols/mists and in Appendix A.

The LOAEL of 0.002 mg chromium(VI)/m³ was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL (LOAEL_{ADJ}) of 0.0005 mg chromium(VI)/m³. The chronic-duration MRL of 5x10⁻⁶ was obtained by dividing the LOAEL_{ADJ} (0.0005 mg chromium(VI)/m³) by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

Few studies have evaluated the effects of chronic inhalation exposure to particulate hexavalent chromium compounds. In workers chronically exposed to inhaled chromium(VI) compounds at 0.0042 mg chromium(VI)/m³, the prevalence of high urinary N-acetyl-β-glucosamidase was increased, indicating possible renal damage (Liu et al. 1998); however, since the chemical form of chromium(VI) was not reported, data from this study are not suitable as the basis for the chronic-duration inhalation MRL specific for particulate hexavalent chromium compounds. The chronic-duration database in animals consists of studies that either did not identify adverse effects of chronic inhalation exposure to particulate hexavalent chromium compounds (Glaser et al. 1986, 1988; Lee et al. 1989) or older studies that did not report sufficient experimental details (Nettesheim and Szakal 1972; Steffee and Baetjer 1965). Thus, due to inadequate data, a chronic-duration inhalation MRL for particulate hexavalent chromium compounds was not derived.

Oral MRLs—Chromium(VI)

Acute. Studies on the acute toxicity of orally-administered chromium(VI) in humans are mostly limited to case reports on ingestion of fatal doses (Clochesy 1984; Iserson et al. 1983; Kaufman et al. 1970; Loubieres et al. 1999; Saryan and Reedy 1988). At lower doses (≥0.036 mg chromium (IV)/kg as potassium dichromate), oral exposure to chromium(VI) has been shown to enhance dermatitis in individuals with known chromium sensitivity (Goitre et al. 1982; Kaaber and Veien 1977).

In animals, acute-duration studies on oral exposure to chromium(VI) compounds have shown effects on hematology and clinical chemistry (NTP 2007, 2008a), male reproductive organs (Li et al. 2001) and development (Elsaieed and Nada 2002; Junaid et al. 1996b); however, the available studies did not

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evaluate comprehensive toxicological end points. Decreased MCV, MCH, and reticulocyte count were observed in rats exposed to ≥ 0.70 mg chromium(VI)/kg/day after 4–5 days of exposure (NTP 2007, 2008a); however, the magnitude of changes was small and may not yet represent an adverse effect of chromium(VI). Significant alterations in the serum activities of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and creatine kinase were observed at ≥ 4.0 – 4.1 mg chromium(VI)/kg/day in rats exposed for 4–5 days (NTP 2007, 2008a). Effects on male reproductive organs, including decreased sperm count, increased percentage of abnormal sperm, and morphological change to seminiferous tubules (decreased diameter of seminiferous tubules and germ cell rearrangement) were observed in Wister rats following a 6-day gavage administration of ≥ 5.2 mg chromium(VI)/kg/day as chromic acid; observations were made 6 weeks after the dosing period (Li et al. 2001). A NOAEL was not defined in this study.

Developmental effects, including increased pre- and postimplantation loss, resorptions, dead fetuses/litter, and skeletal (incomplete ossification of skull bone) and visceral (renal pelvis dilatation) malformations were observed in Wister rats exposed to 8 mg chromium(VI)/kg/day (the only dose tested) as potassium chromate in drinking water (Elsaieed and Nada 2002). Other studies reported total litter loss, decreased viable fetuses and increased resorptions in rats (Bataineh et al. 2007) and increased resorptions in mice (Junaid et al. 1996b) exposed at higher doses.

Results of acute-duration studies in animals show that exposure to oral chromium(VI) compounds may cause hematological (NTP 2007, 2008a), reproductive (Li et al. 2001), and developmental effects (Elsaieed and Nada 2002; Junaid et al. 1996b). However, since the available studies did not evaluate comprehensive toxicological end points, data are inadequate for derivation of an acute-duration oral MRL for chromium(VI). Therefore, an acute-duration oral MRL for hexavalent chromium was not derived.

Intermediate

- An oral MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate (15–364 days) exposure to hexavalent chromium compounds.

Hematological effects (microcytic, hypochromic anemia) in male rats and female mice observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI) for the purpose of derivation of an intermediate-duration oral MRL for chromium(VI) compounds of 0.005 mg chromium(VI)/kg/day. The basis for this determination is as follows.

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No human intermediate-duration studies on chromium(VI) were identified. Numerous animal studies examining systemic, neurological, reproductive, and developmental toxicity have reported effects following oral exposure to chromium(VI) compounds, with hematological effects (microcytic, hypochromic anemia) identified as the most sensitive. Microcytic, hypochromic anemia, characterized by decreased MCV, MCH, Hct, and Hgb, was observed in rats and mice exposed to chromium(VI) compounds in drinking water or feed for intermediate-duration exposures ranging from 22 days to 6 months (NTP 1996a, 1996b, 1997, 2007, 2008a). The lowest reported LOAEL values for hematological effects were 0.77 mg chromium(VI)/kg/day (with a NOAEL value of 0.21 mg chromium(VI)/kg/day) for decreased Hct, Hgb, MCV, and MCH in male rats; and 0.38 mg chromium(VI)/kg/day (a NOAEL was not established) for decreased MCV and MCH in female mice exposed to sodium dichromate dihydrate in drinking water for 22 days (NTP 2008a). Slightly higher LOAEL values were observed for hematological effects in rats and mice exposed to dietary potassium dichromate for 9 weeks (NTP 1996a, 1996b, 1997).

The duration-dependence of hematological effects was evaluated in rats and mice exposed to sodium dichromate dihydrate in drinking water from 23 days up to 6 months (NTP 2007, 2008a). Results of both studies show that the severity of microcytic, hypochromic anemia was dose-dependent, with maximum effects observed after 22–23 days of exposure. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. In female mice, microcytic, hypochromic anemia was also observed, with LOAEL values of 0.38, 1.4, and 3.1 mg chromium(VI)/kg/day at the 22-day, 3-month, and 6-month assessments, respectively, with effects less severe than those observed in rats.

Studies examining systemic toxicity in animals have reported numerous effects, including hepatotoxicity (Achaya et al. 2001; Kumar and Rana 1982, Kumar et al. 1985; NTP 1996a, 2007), gastrointestinal effects (NTP 2007), renal toxicity (Acharya et al. 2001; Diaz-Mayans et al. 1986; Kumar and Rana 1982, 1984), lymphatic and immunological effects (NTP 2007; Snyder and Valle 1991), and decreased body weight (Bataineh et al. 1997; Chowdhury and Mitra 1995; Elbetieha and Al-Hamood 1997; Kanojia et al. 1996, 1998; NTP 2007; Quinteros et al. 2007; Trivedi et al. 1989). However, LOAEL values for these effects were higher than those producing hematopoietic effects. Studies on reproductive toxicity in animals identify the male reproductive system as a target for intermediate-duration exposure to oral chromium(VI) (Aruldas et al. 2004, 2005, 2006; Bataineh et al. 1997; Chowdhury and Mitra 1995; Subramanian et al. 2006; Yousef et al. 2006; Zahid et al. 1990), although these effects are less sensitive

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than hematological effects. In developmental studies in rats and mice, gestational exposure produced increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring; however, these effects were observed high doses (e.g., ≥ 35 mg chromium(VI)/kg/day) (Al-Hamood et al. 1998; Bataineh et al. 2007; Junaid et al. 1996a; Kanojia et al. 1998; Trivedi et al. 1989).

Hematological effects (microcytic, hypochromic anemia) in male rats observed after exposure for 22 days in the NTP (2008a) 2-year study were identified as the most sensitive effect of intermediate-duration oral exposure to chromium(VI). In this study, male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study, with hematological assessments conducted at 22 days, 3 months, 6 months, and 1 year (see Appendix A for a detailed description of study methods and results). To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a) (detailed results of the benchmark dose analysis are provided in Appendix A). Because several hematological parameters are used to define the clinical picture of anemia, the BMDL_{2sd} values for hemoglobin, MCV, and MCH (none of the models provided an adequate fit for hematocrit) were averaged resulting in a BMDL_{2sd} of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average BMDL_{2sd} by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Chronic

- An oral MRL of 0.0009 mg chromium(VI)/kg/day has been derived for chronic (≥ 1 year) exposure to hexavalent chromium compounds.

Nonneoplastic lesions of the duodenum in mice reported in a chronic drinking water study (NTP 2008a) was selected as the critical effect for derivation of a chronic-duration MRL for chromium(VI) compounds of 0.0009 mg chromium(VI)/kg/day. There are limited data on the chronic oral toxicity of chromium in humans. Gastrointestinal effects, including oral ulcer, diarrhea, abdominal pain, and vomiting, were observed in residents living in an area of the People's Republic of China with high chromium(VI) levels in the drinking water. However, the exposure levels associated with these effects is not well characterized. Other ecological studies have examined cancer mortality (Beaumont et al. 2008; Bednar and Kies 1991; Fryzek et al. 2001; Kerger et al. 2009; Linos et al. 2011), but did not report noncarcinogenic effects.

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The chronic-duration oral toxicity database in drinking water in humans consists of ecological studies of an area near a ferrochromium production plant in the Liaoning Province, China comparing cancer mortality in locations that had relatively high or low chromium concentrations in well water (Beaumont et al. 2008; Zhang and Li 1987). Evaluations of cancer mortality rates (cancers deaths per person-year in an 8-year observation period) show that the adjusted stomach cancer mortality rate was higher for the exposed population compared to the control population (Beaumont et al. 2008). However, it was not possible to estimate exposure levels based on the description of the pollution process. Thus, available human data are not adequate as the basis for the chronic-duration oral MRL.

Chronic-duration oral toxicity studies have been conducted in rats and mice (Mackenzie et al. 1958; NTP 2008a). No hematological, hepatic, or renal effects or changes in body weight were observed in study in Sprague-Dawley rats exposed to 3.6 chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (Mackenzie et al. 1958). NTP (2008a) exposed groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study (see Appendix A for a detailed description of all study methods and results). Results of this study identify several chromium(VI)-induced effects, including microcytic, hypochromic anemia, and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas, and salivary gland. Based on comparison of LOAEL values, the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice), and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups (see Appendix A for incidence data for all nonneoplastic lesions). Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL.

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (details of benchmark dose analysis are presented in Appendix A). Based on the lowest BMDL₁₀ value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration MRL of 0.0009 mg chromium(VI)/

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kg/day was derived by dividing the BMDL₁₀ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas and salivary gland).

Inhalation MRLs—Chromium(III)

Acute. Studies evaluating the effects of acute exposure of humans to chromium(III) compounds were not identified. Acute-duration exposure studies in rats and hamsters indicate that the respiratory tract is a target of inhaled chromium(III) compounds (Derelanko et al. 1999; Henderson et al. 1979). Derelanko et al. (1999) evaluated effects of acute exposure to chromium(III) as chromic oxide (insoluble) or basic chromium sulfate (soluble) in rats (5 rats/sex/group) on composition of bronchoalveolar lavage (BAL) fluid. After exposure of rats for 5 days (6 hours/day) to 3, 10, or 30 mg chromium(III)/m³ as chromic oxide (insoluble), analysis of BAL fluid revealed cytoplasmic accumulation of a yellow crystalline material in mononuclear cells of all exposure groups; however, it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein, and BAL fluid activities of β -glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated for 5 days (6 hours/day) with 3, 10, or 30 mg chromium(III)/m³ as basic chromium sulfate (soluble), BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m³ in males. Increased amounts of cellular debris and lysed cells were present in BAL fluid of rats treated with ≥ 3 mg chromium(III)/m³ as basic chromium sulfate (incidence data were not reported). In Syrian hamsters, changes in BAL fluid and lung tissue enzyme activities were observed following exposure to inhaled chromium trichloride for 30 minutes (Henderson et al. 1979); effects included “sporadic changes” in activities of acid phosphatase and alkaline phosphatase in the BAL fluid at 25 mg chromium(III)/m³ and increased acid phosphatase activity in lung tissue at 0.9 mg chromium(III)/m³. In addition, histological examination of the lung revealed focal accumulations of macrophages and polymorphonuclear cells. However, it is not clear that the effects observed in this study are toxicologically significant. Thus, results of acute-duration studies in rats and hamsters show that inhaled chromium(III) compounds produce alterations in BAL fluid composition and lung tissue enzyme activities; however, data are not adequate to characterize the exposure-response relationship for respiratory effects. Therefore, an acute-duration inhalation MRL for trivalent chromium was not derived.

Intermediate. Studies evaluating the effects of intermediate-duration exposure of humans to chromium(III) compounds were not identified. In animals exposed to inhaled chromium(III) compounds for intermediate durations, the respiratory tract has been identified as the primary target organ, based on results of a 13-week study in rats exposed to chromic oxide (insoluble) or basic chromium sulfate (soluble) (Derelanko et al. 1999). In this study, which examined comprehensive toxicological end points, male and female CDF rats (15/sex/group) were exposed by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m³ as chromic oxide or as basic chromium sulfate for 6 hours/day, 5 days/week for 13 weeks. Of the 15 rats/sex/group, 10 rats/sex/group were sacrificed after 13 weeks of exposure and 5 rats/sex/group were sacrificed after an additional 13-week recovery period (e.g., no exposure). Assessments made in this study included mortality; clinical signs of toxicity; body weight; hematology; clinical chemistry; urinalysis; sperm morphology, count and motility; gross necropsy; microscopic examination of comprehensive tissues for all animals in the control and 30 mg chromium(III)/m³ groups; and microscopic examination of respiratory tissues (nasal tissues, trachea, lungs, larynx, and mediastinal and mandibular lymph nodes) in all animals. Both chromic oxide and basic chromium sulfate produced adverse respiratory effects (histopathological changes to respiratory tissues and increased lung weights) in male and female rats, with no adverse effects in other tissues. However, differences between the two compounds were observed with respect to severity and location of respiratory effects; effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung, and respiratory lymph tissues). The study authors suggested that differences in the respiratory toxicity of these compounds may be related to differences in chemical-physical properties (e.g., solubility, acidity). The only other intermediate-duration inhalation study in animals was conducted in rabbits exposed to 0.6 mg chromium(III)/m³ as chromium nitrate for 4–6 weeks (6 hours/day, 5 days/week) (Johansson et al. 1986b). Results of this study showed effects on pulmonary macrophages (altered functional and metabolic activities); however, the toxicological significance of this finding is uncertain and animals were not examined for other effects. Thus, the 13-week inhalation study by Derelanko et al. (1999) was selected as the critical study for derivation of intermediate-duration inhalation MRLs for chromium(III) compounds. Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, distinct intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds. Additional details of respiratory effects produced by chromic oxide and basic chromium sulfate are described below under derivation of intermediate-duration inhalation MRLs for insoluble trivalent chromium compounds and for soluble trivalent chromium compounds, respectively.

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- An inhalation MRL of 0.005 mg chromium(III)/m³ has been derived for intermediate (15–364 days) exposure to insoluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled insoluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to chromic oxide for 13 weeks, with histopathological changes to the respiratory lymphatic tissue occurring at ≥ 3 mg chromium(III)/m³ and to the lung at ≥ 10 mg chromium(III)/m³. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m³, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes (severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx.

For evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m³ for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following a 13-week posttreatment recovery period, trace-to-mild septal cell hyperplasia and trace-to-mild chronic interstitial inflammation of the lung were observed at ≥ 3 mg chromium(III)/m³ in males and at ≥ 10 mg chromium(III)/m³ in females. In addition, pigmented macrophages and black pigment in peribronchial lymphatic tissues and the mediastinal lymph node in animals from all treatment groups were also observed; this finding, although not considered adverse, indicates that the test material had not been completely cleared from the lung during the treatment-free recovery period. Thus, for evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (based on severity) of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

The LOAEL of 3 mg chromium(III)/m³ for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were considered as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A benchmark concentration for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. To determine the point of departure, the LOAEL value of 3 mg chromium(III)/m³

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was first adjusted for intermittent and converted to human equivalent concentrations (LOAEL_{HEC}) (see Appendix A for details).

Based on the lowest LOAEL_{HEC} of 0.43 mg chromium(III)/m³, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats were selected as the critical effect. The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m³ was derived by dividing the minimal LOAEL_{HEC} of 0.43 mg chromium(III)/m³ by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

- An inhalation MRL of 0.0001 mg chromium(III)/m³ has been derived for intermediate (15–364 days) exposure to soluble trivalent chromium particulate compounds.

The lung and respiratory lymphatic tissues were identified as the target tissues for inhaled soluble trivalent chromium particulate compounds, based on observations reported in the study by Derelanko et al. (1999) (as discussed above). Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at ≥ 3 mg chromium(III)/m³. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes, and cellular debris; foci of “intense” inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation, and suppurative and mucoid exudates of nasal tissues and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Thus, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were evaluated to determine the specific end point for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used, with adjustment of the LOAEL for intermittent exposure and human equivalent concentrations (see Appendix A for details). Data for relative lung weights in males and females (presented in Appendix A) were modeled using all available continuous-variable models in the EPA Benchmark Dose program

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(version 1.4.1). The BMC and the 95% lower confidence limit (BMCL) calculated were estimated for doses associated with a change of 1 standard deviation from the control mean ($\text{BMCL}_{1\text{sd}}$). The $\text{BMCL}_{1\text{sd}}$ values for the best fitting models in male and female rats were adjusted for intermittent exposure and human equivalent concentrations, yielding $\text{BMCL}_{1\text{sd}, \text{HEC}}$ values of 0.17 and 0.34 mg chromium(III)/ m^3 in males and females, respectively (see Appendix A for detail of benchmark dose analysis).

Based on comparison of $\text{LOAEL}_{\text{HEC}}$ values for respiratory tract lesions and $\text{BMCL}_{1\text{sd}, \text{HEC}}$ values for increased lung weight, the lowest value of 0.04 mg chromium(III)/ m^3 (the $\text{LOAEL}_{\text{HEC}}$ for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/ m^3 was derived by dividing the $\text{LOAEL}_{\text{HEC}}$ of 0.04 mg chromium(III)/ m^3 by a composite uncertainty factor of 300 (10 for use of a LOAEL , 3 for pharmacodynamic variability between animals to humans, and 10 for human variability). It should not be concluded from comparison of the intermediate-duration MRLs for soluble particulate chromium(VI) and soluble particulate chromium(III) compounds that chromium(III) is more toxic than chromium(VI).

The respiratory tract is the major target of inhalation exposure to chromium compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. For chronic exposure of humans, the available occupational studies for exposure to chromium(III) compounds include or likely include concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors in estimating exposure levels for these effects for the purpose of deriving MRLs.

Chronic. No studies evaluating the effects of chronic-duration inhalation exposure of animals to chromium(III) compounds alone were identified. Exposure to mixtures of chromium(VI) and chromium(III) compounds (3:2 mixture of chromium(VI) trioxide and chromium(III) oxide) have resulted in adverse respiratory effects in Wistar rats, including increased lung weight and histopathological changes to lung tissues (interstitial fibrosis and thickening of the septa of the alveolar lumens; Glaser et al. 1986, 1988). However, these data not appropriate as the basis for a chronic-duration inhalation MRL for chromium(III) compounds due to concomitant exposure to chromium(VI).

Oral MRLs—Chromium(III)

No acute-, intermediate-, or chronic-duration oral MRLs were derived for chromium(III) because studies evaluating the effects of chromium(III) in humans and animals following acute, intermediate, and chronic oral exposure were inadequate for establishing the exposure concentrations associated with adverse health effects (as discussed below). The IOM has recommended an adequate intake level of 20–45 µg chromium(III) for adolescents and adults, equivalent to 0.28–0.64 µg chromium(III)/kg/day (0.0003–0.0006 mg chromium(III)/kg/day), assuming a 70-kg body weight (IOM 2001).

Little information is available on the effects of acute-duration oral exposure to chromium(III) compounds. Information on the effects of intermediate-duration oral exposure of humans is limited to case reports of renal failure (Wani et al. 2006; Wasser et al. 1997) and rhabdomyolysis (Martin and Fuller 1998) following ingestion of dietary supplements containing chromium(III). In animals, acute exposure of rats to dietary chromium(III) picolinate did not produce alterations in hematology or clinical chemistry. Following acute exposure of mated rats, an increase in total litter loss was observed in female rats (at 33.6 mg chromium(III)/kg/day) (Bataineh et al. 2007). In a study evaluating effects of chromium(III) on maturation of the reproductive system in mice (74 mg chromium(III)/kg/day), significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) and a significant delay in timing of vaginal opening in the female offspring were observed (Al-Hamood et al. 1998). However, gestational exposure studies on chromium(III) compounds were conducted at high daily doses and do not provide sufficient information to characterize the dose-response relationship for adverse developmental effects. Thus, the data are inadequate for derivation of an acute-duration oral MRL.

Information on adverse effects of intermediate-duration oral exposure of humans to chromium(III) compounds was not identified. Results of most animal studies show no adverse effects associated with intermediate-duration oral exposure to chromium(III) compounds (chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate, and chromium potassium sulfate) (Anderson et al. 1997b; De Flora et al. 2006; Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007), even at very high daily doses. In the study conducted by NTP (2008b; Rhodes et al. 2005), daily doses of up to 506 and 1,415 mg chromium(III)/mg/day as chromium picolinate were evaluated in rats and mice, respectively, and in the Ivankovic and Preussmann (1975) study, daily doses up to 1,806 mg chromium(III)/kg/day as chromium oxide were evaluated in rats.

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Adverse reproductive effects have been reported following intermediate-duration exposure of animals to chromium(III) as chromium chloride administered by gavage or in drinking water. A series of studies by the same research group evaluated reproductive effects of exposure to chromium(III) as chromium chloride in drinking water for 12 weeks (Al-Hamood et al. 1998; Bataineh et al. 1997, 2007; Elbetieha and Al-Hamood 1997). Reproductive effects observed included alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats (40 mg chromium(III)/kg/day; only dose tested) (Bataineh et al. (1997); decreased number of pregnant female Swiss mice following the mating of unexposed females to exposed males (13 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997); impaired fertility in exposed female mice (5 mg chromium(III)/kg/day) mated to unexposed males (Elbetieha and Al-Hamood 1997); and increased testes and ovarian weights and decreased preputial gland and uterine weights in mice (5 mg chromium(III)/kg/day) (Elbetieha and Al-Hamood 1997). Results of the study by Elbetieha and Al-Hamood (1997) should be interpreted with caution due to concerns regarding experimental methods, including decreased water consumption in the higher concentration group (resulting in a potential overestimate of exposure and uncertainty regarding daily dose calculations); the study was not conducted using a standard mating protocol; sperm counts were not conducted; and the definition and classification of non-viable fetuses was not described. Decreased spermatogenesis was observed in BABL/c mice treated with 9.1 mg chromium(III)/kg/day as chromium sulfate in drinking water for 7 weeks (Zahid et al. 1990); however, sensitivity of methods used to evaluate spermatogonia in this study have been questioned by NTP (1996a). NOAEL values for reproductive effects were not identified in these studies. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. The average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for male mice and were 0.35, 1.05, 2.1, and 8.4 mg/kg/day for rats (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c, and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

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In contrast to the reproductive effects of chromium chloride in drinking water, dietary exposure to chromium(III) picolinate has not been associated with reproductive effects. Exposure to chromium picolinate in the diet for 3 months did not produce adverse effects on reproductive tissues, as assessed by organ weights, gross and histopathological examinations, sperm count, sperm motility, duration of estrous cycle stages and estrous cycle length at doses up to 505 and 506 mg chromium(III)/kg/day in male and female rats, respectively, or at doses up to 1,415 and 1,088 mg chromium(III)/kg/day in male and female mice (NTP 2008b). No morphological changes to reproductive organs, as assessed by histopathological examination, were observed in male and female Sprague-Dawley rats exposed to chromium nicotinate in the diet at 1.2 and 1.5 mg chromium(III)/kg/day, respectively for 2 months or at 0.22 and 0.25 mg chromium(III)/kg/day, respectively for 1 year (Shara et al. 2005, 2007). In summary, conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed) or to differences in toxic potency of the specific chromium(III) compounds evaluated. Thus, available data are not sufficient to define the dose-response relationship for adverse reproductive effects of chromium(III) compounds.

Little information is available on the potential developmental effects of chromium(III) compounds. No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975).

Results of studies in animals exposed to oral chromium(III) compounds indicate that adverse reproductive effects may occur. However, the available data do not identify NOAEL values for effects and, therefore, are not sufficient to characterize the dose-response relationship. Thus, data are inadequate for derivation of an intermediate-duration oral MRL.

Chronic-duration studies on oral exposure of humans to chromium(III) compounds were not identified. Several animal studies show no adverse effects associated with chronic-duration oral exposure to chromium(III) compounds (chromium acetate, chromium chloride, chromium nicotinate, chromium oxide, chromium picolinate) (Ivankovic and Preussmann 1975; Mackenzie et al. 1958; Schroeder et al. 1965; Shara et al. 2007), even at very high daily doses. Thus, in the absence of data showing adverse effects of chronic oral exposure, a chronic-duration oral MRL for chromium(III) compounds was not derived.

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A summary of the inhalation and oral MRLs for chromium(VI) and chromium(III) is presented in [Table 2-1](#).

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Table 2-1. Summary of MRL Values for Chromium(VI) and Chromium(III)

	Point of departure	UF	MRL
Inhalation MRLs			
Chromium(VI)			
Acute	Insufficient data to derive MRL		
Intermediate			
Aerosols and mists	LOAEL of 0.002 mg Cr/m ³ for nasal irritation, mucosal atrophy, impaired lung function in workers (Lindberg and Hedenstierna 1983)	100	5x10 ⁻⁶ mg Cr/m ³
Particulates	BMCL ₁₀ of 0.016 mg Cr/m ³ (converted to a BMCL _{HEC} of 0.010 mg Cr/m ³) based on alterations in lactate dehydrogenase levels in BAL in rats (Glaser et al. 1990)	30	3x10 ⁻⁴ mg Cr/m ³
Chronic			
Aerosols and mists	LOAEL of 0.002 mg Cr/m ³ for nasal irritation, mucosal atrophy, impaired lung function in workers (Lindberg and Hedenstierna 1983)	100	5x10 ⁻⁶ mg Cr/m ³
Particulates	Insufficient data to derive MRL		
Chromium(III)			
Acute	Insufficient data to derive MRL		
Intermediate			
Insoluble particulates	LOAEL of 3 mg Cr/m ³ (adjusted to 0.54 mg Cr/m ³ for 90 intermittent exposure and converted to a LOAEL _{HEC} of 0.43 mg Cr/m ³) for septal cell hyperplasia and chronic interstitial inflammation of the lungs in rats (Derelanko et al. 1999)	90	5x10 ⁻³ mg Cr/m ³
Soluble particulates	LOAEL of 3 mg Cr/m ³ (adjusted to 0.54 mg Cr/m ³ for 300 intermittent exposure and converted to a LOAEL _{HEC} of 0.04 mg Cr/m ³) for nasal and larynx lesions in rats (Derelanko et al. 1999)	300	1x10 ⁻⁴ mg Cr/m ³
Chronic	Insufficient data to derive MRL		
Oral MRLs			
Chromium(VI)			
Acute	Insufficient data to derive MRL		
Intermediate	BMDL _{2SD} of 0.52 mg Cr/kg/day for microcytic, hypochromic anemia in rats (NTP 2008a)	100	0.005 mg/kg/day
Chronic	BMDL ₁₀ of 0.09 mg Cr/kg/day for diffuse epithelial hyperplasia of the duodenum in mice (NTP 2008a)	100	9x10 ⁻⁴ mg Cr/kg/day
Chromium(III)			
Acute	Insufficient data to derive MRL		
Intermediate	Insufficient data to derive MRL		
Chronic	Insufficient data to derive MRL		

BAL = bronchoalveolar lavage; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; UF = uncertainty factor

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of chromium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Chromium is a naturally occurring element found in animals, plants, rocks, and soil and in volcanic dust and gases. Chromium has oxidation states (or "valence states") ranging from chromium(-II) to chromium(VI). Elemental chromium (chromium(0)) does not occur naturally. Chromium compounds are stable in the trivalent (III) state and occur in nature in this state in ores, such as ferrochromite. The hexavalent (VI) form is the second-most stable state. However, chromium(VI) rarely occurs naturally, but is usually produced from anthropogenic sources (EPA 1984a).

Trivalent chromium compounds, except for acetate, nitrate, and chromium(III) chloride-hexahydrate salts, are generally insoluble in water. Some hexavalent compounds, such as chromium trioxide (or chromic acid) and the ammonium and alkali metal (e.g., sodium, potassium) salts of chromic acid are readily soluble in water. The alkaline metal (e.g., calcium, strontium) salts of chromic acid are less soluble in water. The zinc and lead salts of chromic acid are practically insoluble in cold water. Chromium(VI) compounds are reduced to chromium(III) in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, chromium(VI) compounds are more stable (EPA 1984a). For more information on the physical and chemical properties of chromium, see Chapter 4.

In humans and animals, chromium(III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism by potentiating the action of insulin (Anderson 1981). The biologically active form of chromium, called chromodulin, is an oligopeptide complex containing with four chromic ions (Jacquemet et al. 2003). Both humans and animals are capable of converting inactive inorganic chromium(III) compounds to physiologically active forms. The nutritional role of chromium is further discussed in Section 3.4.3. Although chromium(III) has been reported to be an essential nutrient, exposure to high levels via inhalation, ingestion, or dermal contact may cause some adverse health effects. Most of the

studies on health effects discussed below involve exposure to chromium(III) and chromium(VI) compounds. In addition, chromium(IV) was used in an inhalation study to determine permissible exposure levels for workers involved in producing magnetic tape (Lee et al. 1989).

Several factors should be considered when evaluating the toxicity of chromium compounds. The purity and grade of the reagent used in the testing is an important factor. Both industrial- and reagent-grade chromium(III) compounds can be contaminated with small amounts of chromium(VI) (Levis and Majone 1979). Thus, interpretation of occupational and animal studies that involve exposure to chromium(III) compounds is difficult when the purity of the compounds is not known. In addition, it is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes and in the gastric environment (Petrilli et al. 1986b; Samitz 1970). However, whereas chromium(VI) can readily be transported into cells, chromium(III) is much less able to cross cell membranes. The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium compounds, whereas the reduction of chromium(VI) to chromium(III) outside of cells is a major mechanism of protection.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be

insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) are indicated in [Tables 3-1 and 3-4](#) and [Figures 3-1 and 3-3](#) for chromium(VI).

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Due to the extremely high boiling point of chromium, gaseous chromium is rarely encountered. Rather, chromium in the environment occurs as particle-bound chromium or chromium dissolved in droplets. As discussed in this section, chromium(VI) trioxide (chromic acid) and soluble chromium(VI) salt aerosols may produce different health effects than insoluble particulate compounds. For example, exposure to chromium(VI) trioxide results in marked damage to the nasal mucosa and perforation of the nasal septum, whereas exposure to insoluble(VI) compounds results in damage to the lower respiratory tract.

3.2.1.1 Death

No studies were located regarding death in humans after acute inhalation of chromium or chromium compounds. An increased risk of death from noncancer respiratory disease was reported in retrospective

3. HEALTH EFFECTS

mortality studies of workers in a chrome plating plant (Sorahan et al. 1987) and chromate production (Davies et al. 1991; Taylor 1966) (see Section 3.2.1.2, Respiratory Effects). However, a number of methodological deficiencies in these studies prevent the establishment of a definitive cause-effect relationship. Retrospective mortality studies associating chromium exposure with cancer are discussed in Section 3.2.1.7.

Acute inhalation LC_{50} values in rats for several chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 29 to 45 mg chromium(VI)/ m^3 for females and from 33 to 82 mg chromium(VI)/ m^3 for males (Gad et al. 1986). Acute inhalation LC_{50} values for chromium trioxide were 87 and 137 mg chromium(VI)/ m^3 for female and male rats, respectively (American Chrome and Chemicals 1989). Female rats were more sensitive than males to the lethal effects of most chromium(VI) compounds except sodium chromate, which was equally toxic in both sexes. Signs of toxicity included respiratory distress, irritation, and body weight depression (Gad et al. 1986). The LC_{50} values for chromium(VI) are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#).

3.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to chromium or its compounds. Respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, body weight, and metabolic effects are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#) for chromium(VI) and recorded in [Table 3-2](#) and plotted in [Figure 3-2](#) for chromium(III).

Respiratory Effects. The respiratory tract in humans is a major target of inhalation exposure to chromium compounds. Chromate sensitive workers acutely exposed to chromium(VI) compounds may develop asthma and other signs of respiratory distress. Five individuals who had a history of contact dermatitis to chromium were exposed via a nebulizer to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. A 20% decrease in the forced expiratory volume of the lungs was observed and was accompanied by erythema of the face, nasopharyngeal pruritus, nasal blocking, coughing, and wheezing (Olaguibel and Basomba 1989).

Dyspnea, cough, and wheezing were reported in two cases in which the subjects inhaled "massive amounts" of chromium(VI) trioxide. Marked hyperemia of the nasal mucosa without nasal septum

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
			NOAEL (mg/m³)	Less Serious (mg/m³)		
ACUTE EXPOSURE						
Death						
1	Rat (Fischer- 344)	4 hr				American Chrome and Chemicals 1989 CrO3 (VI)
2	Rat (Fischer- 344)	4 hr				Gad et al. 1986 (NH4)2Cr2O7 (VI)
3	Rat (Fischer- 344)	4 hr				Gad et al. 1986 K2Cr2O7 (VI)
4	Rat (Fischer- 344)	4 hr				Gad et al. 1986 Na2Cr2O7.2H2O (VI)
5	Rat (Fischer- 344)	4 hr				Gad et al. 1986 Na2CrO4 (VI)
Systemic						
6	Rat (Sprague- Dawley)	10 d 5 d/wk 6 hr/d	0.49 M	1.15 M (nasal hemorrhage)		Kim et al. 2004 CrO3 (VI)
INTERMEDIATE EXPOSURE						
Systemic						
7	Human	<90 d (occup)		0.025 M (irritated nasal septum)		Gibb et al. 2000a CrO3 (VI)

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
8	Human	Resp	0.033 M	perforated nasal septum		Gibb et al. 2000a CrO3 (VI)	
		Other					
9	Human	Resp	0.1	(epitaxis rhinorrhea, nasal ulceration and perforation)		Gomes 1972 CrO3 (VI)	
10	Human	Resp	0.09 M	(epitaxis, rhinorrhea ulceration of nasal septum)		Kleinfield and Rosso 1965 CrO3 (VI)	
11	Human	Resp	0.002 ^b	(nasal mucosa atrophy and ulceration, mild decreased lung function)		Lindberg and Hedenstierna 1983 CrO3 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
12 Rat (Wistar)	28 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
		Gastro	0.2 M				
		Hemato	0.2 M				
		Hepatic	0.2 M				
		Renal	0.2 M				
		Bd Wt	0.2 M				
13 Rat (Wistar)	90 d 7 d/wk 22 hr/d	Resp		0.025 M (increased percentage of lymphocytes in bronchial alveolar lavage fluid)		Glaser et al. 1985 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
		Gastro	0.2 M				
		Hemato	0.2 M				
		Hepatic	0.1 M	0.2 M (increased levels of serum phospholipids and triglycerides)			
		Renal	0.2 M				
		Bd Wt	0.2 M				

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)			
14	Rat (Wistar)	30 or 90 d 7 d/wk 22 hr/d	Resp		0.05 M ^c (increased lung weight, hyperplasia, macrophage infiltration, increased protein, albumin, lactate dehydrogenase in BAL fluid)			Glaser et al. 1990 Na2Cr2O7.2H2O (VI)	
			Gastro	0.4 M					
			Hemato		0.05 M (increased white blood cell count)				
			Hepatic	0.4 M					
			Renal	0.4 M					
			Bd Wt	0.1 M	0.2 M (28% decreased body weight gain)				
15	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	0.23 M	0.49 M (inflammation and macrophage aggregation in alveolar regions of the lung)			Kim et al. 2004 CrO3 (VI)	
			Cardio	1.15 M					
			Hemato		0.23 M (decreased hematocrit)				
			Hepatic	1.15 M					
			Renal	1.15 M					
			Endocr	1.15 M					
			Bd Wt	1.15 M					

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
16	Mouse (C57BL) 12 mo 2 d/wk 120 min/d	Resp			1.81 F (emphysema, nasal septum perforation)	Adachi 1987 CrO3 (VI)	
17	Mouse (ICR) 12 mo 2 d/wk 30 min/d	Resp			3.63 F (emphysema, nasal septum perforation)	Adachi et al. 1986 CrO3 (VI)	
18	Rabbit (NS) 4-6 wk 5 d/wk 6 hr/d	Resp	0.9 M			Johansson et al. 1986b Na2CrO4 (VI)	
19	Immuno/ Lymphoret Rat (Fischer- 344) 2-4 wk 5 d/wk 5 hr/d			0.36 (increased neutrophils, monocytes, and decreased macrophages in BAL fluid; decreased cytokine levels)		Cohen et al. 1998 K2CrO4 (VI)	
20	Rat (Fischer- 344) 2-4 wk 5 d/wk 5 hr/d			0.36 (decreased tumor necrosis factor-alpha levels and production of superoxide anion and hydrogen peroxide and increased nitric oxide production)		Cohen et al. 1998 BaCrO4 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
21	Rat (Wistar) 28 d 7 d/wk 22 hr/d			0.025 M (increased response to sheep red blood cells, increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
22	Rat (Wistar) 90 d 7 d/wk 22 hr/d			0.025 M (increased response to sheep RBC, increased % of lymphocytes in bronchoalveolar lavage fluid, increased % of macrophages in telophase, increased activity of macrophages)		Glaser et al. 1985 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
Neurological							
23	Rat (Sprague- Dawley) 13 wk 5 d/wk 6 hr/d		1.15 M			Kim et al. 2004 CrO ₃ (VI)	
Reproductive							
24	Rat (Wistar) 90 d 7 d/wk 22 hr/d		0.2 M			Glaser et al. 1985 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
25	Rat (Sprague- Dawley) 13 wk 5 d/wk 6 hr/d		1.15 M			Kim et al. 2004 CrO ₃ (VI)	
CHRONIC EXPOSURE							
Systemic							
26	Human 7 yr avg 5 d/wk 8 hr/d (occup)	Renal		0.05 M (increase in retinol binding protein and tubular antigen)		Franchini and Mutti 1988 CrO ₃ (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
27	Human	>1 yr (occup)		0.025 M (bleeding nasal septum)		Gibb et al. 2000a CrO3 (VI)	
		Ocular		0.049 M			
28	Human	(occup)		0.414 (nasal septum perforation, chronic pharyngitis, atrophy of larynx)		Hanslian et al. 1967 CrO3 (VI)	
		Resp					
		Gastro		0.414 (chronic tonsillitis)			
29	Human	0.2-23.6 yr avg 2.5 yr 5 d/wk 8 hr/d (occup)		0.002 ^b (nasal mucosa atrophy and ulceration, mild decreased lung function)		Lindberg and Hedenstierna 1983 CrO3 (VI)	
30	Human	0.1-26 yr 5.3 yr avg 5 d/wk 8 hr/d (occup)		0.004 M (increased urinary beta-2-microglobulin)		Lindberg and Vesterberg 1983b CrO3 (VI)	
31	Human	(occup)		0.0042 (increased prevalence of high N-acetyl-B-glucosaminidase levels)		Liu et al. 1998 Cr(VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
32	Human 7.5 yr avg (range 3-16 yr) (occup)	Resp		0.004 M (epitaxis, rhinorrhea, nasal septum ulceration and perforation)		Lucas and Kramkowski 1975 CrO3 (VI)	
33	Rat (Wistar) 18 mo 7 d/wk 22 hr/d	Resp	0.1 M			Glaser et al. 1986, 1988 Na2Cr2O7.2H2O (VI)	
		Hemato	0.1 M				
		Hepatic	0.1 M				
		Renal	0.1 M				
		Endocr	0.1 M				
		Bd Wt	0.1 M				
34	Rat (Wistar) 2 yr 4 d/wk 4-5 hr/d	Resp			1.6 (granulomata, giant cells, bronchopneumonia, abscesses)	Steffee and Baetjer 1965 Finely ground chromium roast (VI)	
35	Mouse (C57BL/6) 18 mo 5 d/wk 5.5 hr/d	Resp			4.3 (epithelial necrosis, hyperplasia)	Nettesheim and Szakal 1972 CaCrO4 (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		
36	Gn Pig (NS) 4.5 yr 4 d/wk 4-5 hr/d	Resp			1.6	Steffe and Baejer 1965 Mixed chromium roast K ₂ Cr ₂ O ₇ , Na ₂ CrO ₄ (VI)	
Immuno/ Lymphoret							
37	Human 5.8 yr (Occup)		0.001	(increased response of peripheral blood mononucleocytes to concanavalin A)		Mignini et al. 2004 Cr (VI)	
Cancer							
38	Human 1 mo- 29 yr 5 d/wk 8 hr/d (occup)				0.5 M (CEL: lung cancer)	Hayes et al. 1989 PbCrO ₄ and ZnCrO ₄ (VI)	
39	Human 4-19 yr 5 d/wk 8 hr/d (occup)				0.5 (CEL: lung cancer)	Langård and Norseth 1975 PbCrO ₄ and ZnCrO ₄ (VI)	
40	Human 1-7 yr 5 d/wk 8 hr/d (occup)				0.25 (CEL: lung cancer)	Mancuso 1975 Soluble Cr(VI)	
41	Human 1 mo- 29 yr 5 d/wk 8 hr/d (occup)				0.1 M (CEL: lung cancer)	Sheffet et al. 1982 PbCrO ₄ and ZnCrO ₄ (VI)	

Table 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/m ³)	Less Serious (mg/m ³)	Serious (mg/m ³)		
42	Rat (Wistar) 18 mo 7 d/wk 22 hr/d				0.1 M (CEL: lung tumors)	Glaser et al. 1986, 1988 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
43	Mouse (C57BL/6) 18 mo 5 d/wk 5 hr/d				4.3 (CEL: alveogenic adenomas and adenocarcinomas)	Nettesheim et al. 1971 CaCrO ₄ (VI)	

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate and chronic inhalation minimal risk level (MRL) of 0.000005 mg chromium(VI)/m³ for dissolved chromium (VI) aerosols and mists.. Exposure concentration adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for human variability and 10 for extrapolating from a LOAEL).

c Used to derive an intermediate inhalation minimal risk level (MRL) of 0.0003 mg chromium(VI)/m³ for particulate hexavalent chromium. Benchmark concentration of 0.016 mg chromium (VI)/m³ was divided by an uncertainty factor of 30 (3 extrapolation from animals to humans using dosimetric adjustments and 10 for human variability).

avg = average; BAL = bronchoalveolar lavage; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NS = not specified; NOAEL = no-observed-adverse-effect level; occup = occupational; RBC = red blood cell; Resp = respiratory; wk = week(s); x = times; yr = year(s)

Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation

Acute (≥14 days)

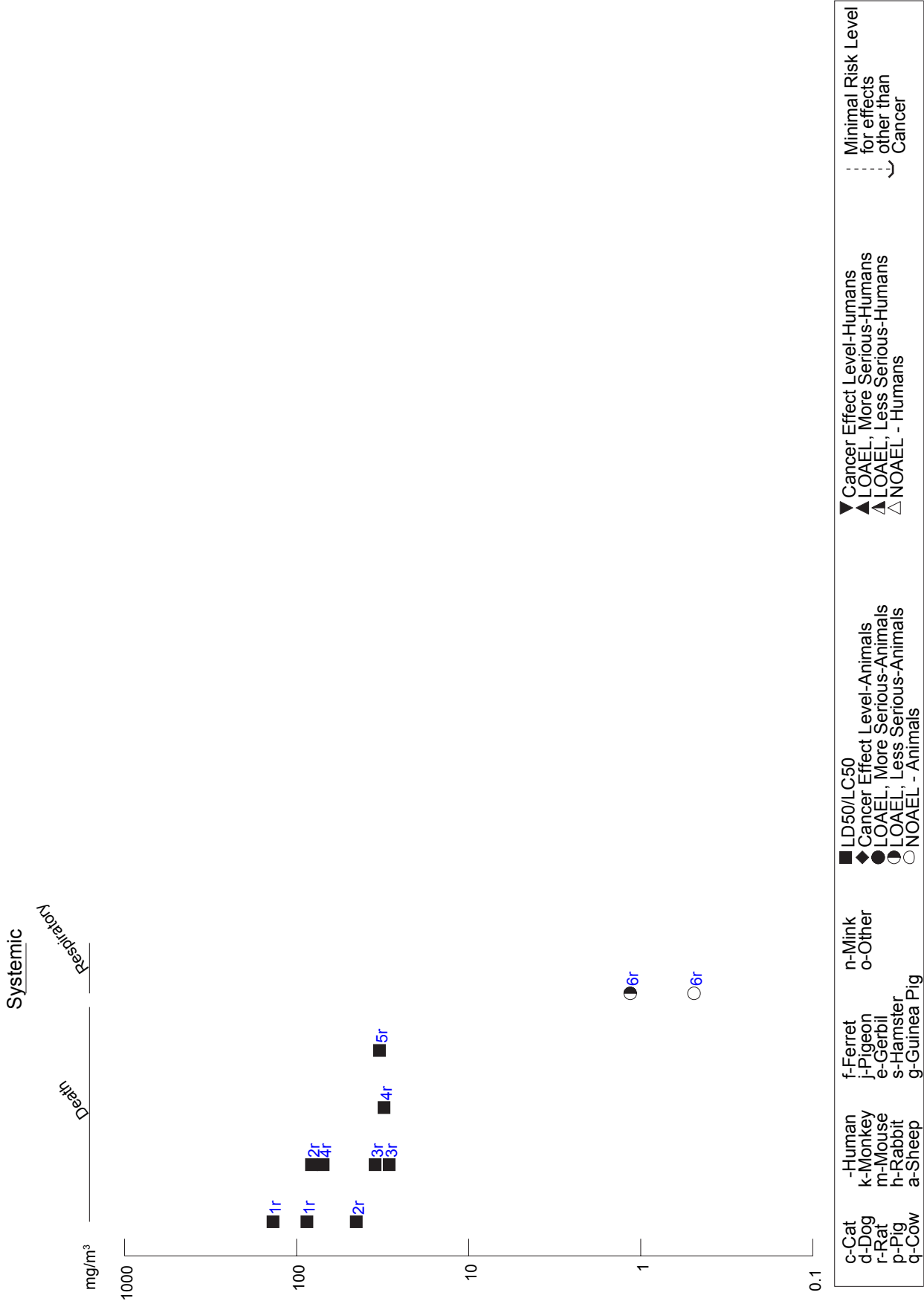


Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (Continued)

Intermediate (15-364 days)

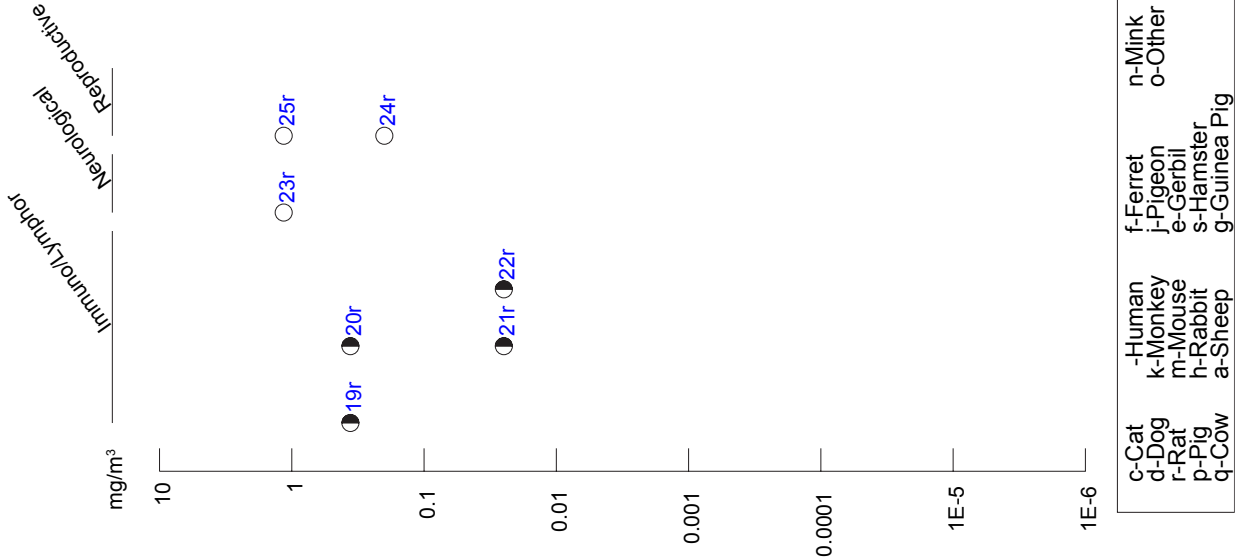


Figure 3-1 Levels of Significant Exposure to Chromium VI - Inhalation (Continued)

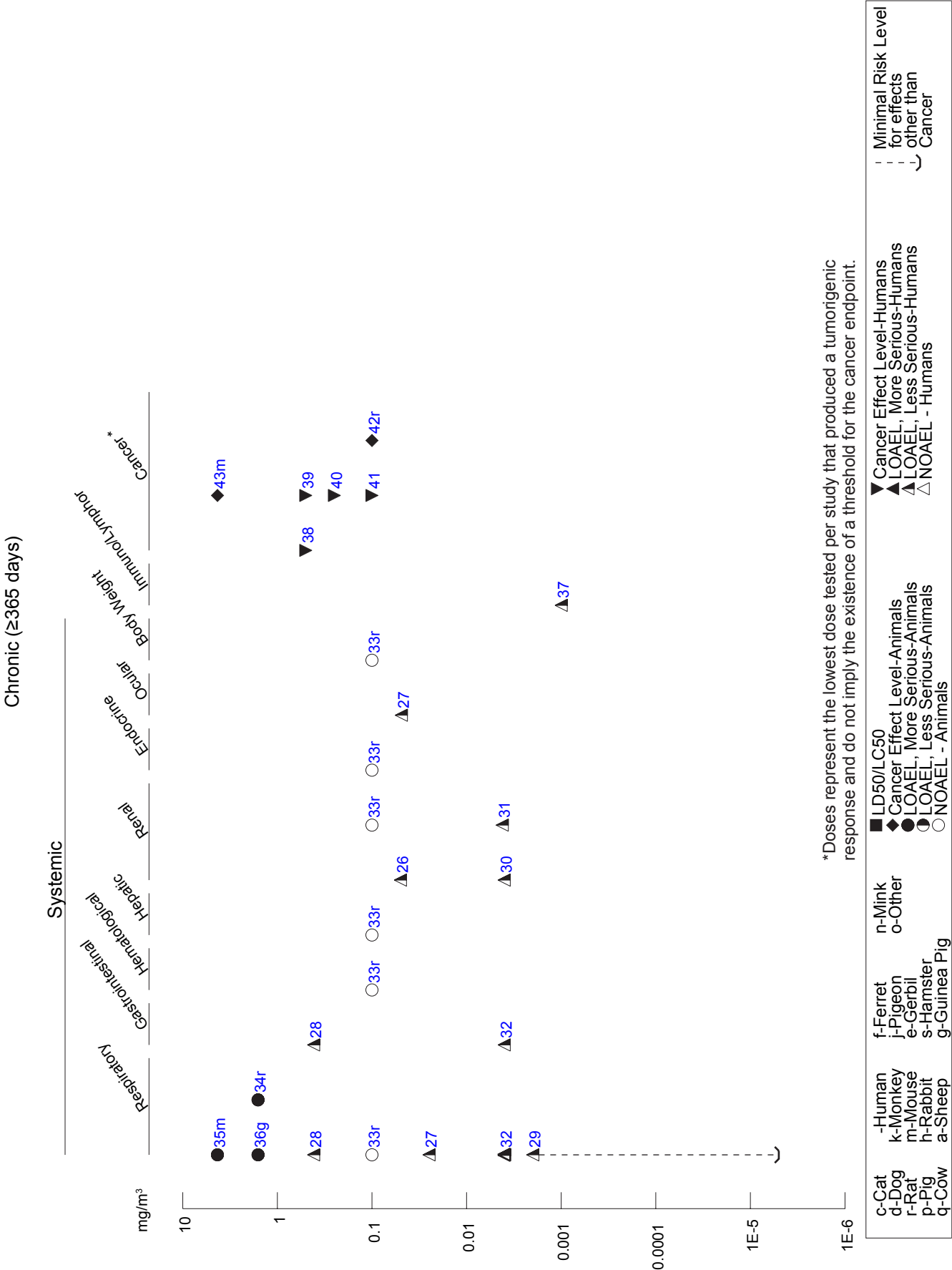


Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference	Comments
					Less Serious (mg/m³)	Serious (mg/m³)		
ACUTE EXPOSURE								
Systemic								
1	Hamster (Syrian)	30 min	Resp		0.9	(increased acid phosphatase activity in lung tissue)	Henderson et al. 1979 CrCl3 (III)	
INTERMEDIATE EXPOSURE								
Systemic								
2	Rat (CDF)	13 wk 6 hr/d 5 d/wk	Resp	3 F	^b 3 M	(septal cell hyperplasia and interstitial inflammation of the lung; increased absolute and relative lung weight at 30 mg/m3)	Derelanko et al. 1999 Cr2O3 (III)	
					10 F	(interstitial inflammation and hyperplasia of alveolar septa)		
			Cardio	30				
			Gastro	30				
			Hemato	30				
			Hepatic	30				
			Renal	30				
			Endocr	30				
			Ocular	30				
			Bd Wt	30				

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m³)	Serious (mg/m³)		
3	Rat (CDF)	13 wk 6 hr/d 5 d/wk	Resp	3	(inflammation of lung; nasal tissues and larynx lesions; increased lung weight)	Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	
4	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp	0.6 M (decreased macrophage activity)	10 M (~10% decreased in body weight)	Johansson et al. 1986b Cr(NO3)39H2O(III)	
Immuno/ Lymphoret							
5	Rat (CDF)	13 wk 6 hr/d 5 d/wk	3	(hyperplasia of mediastinal lymph node)		Derelanko et al. 1999 Cr2O3 (III)	
6	Rat (CDF)	13 wk 6 hr/d 5 d/wk	3	(histiocytosis, lymphoid hyperplasia and enlargement of peribronchial and mediastinal lymph nodes)		Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m³)	Serious (mg/m³)		
Neurological							
7 Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	
8 Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2O3 (III)	Increased absolute and relative lung weight in males at 30 mg/m3.
Reproductive							
9 Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2O3 (III)	
10 Rat (CDF)	13 wk 6 hr/d 5 d/wk		30			Derelanko et al. 1999 Cr2(OH)x(SO4)yNaSO4.2H2O (III)	
CHRONIC EXPOSURE							
Systemic							
11 Human	2-12 yr 5 d/wk 8 hr/d (occup)	Renal	0.075 M			Foa et al. 1988 Cr2O3 (III)	
12 Human	(occup)	Resp	1.99			Korallus et al. 1974a Cr2O3 and Cr2(SO4)3 (III)	

Table 3-2 Levels of Significant Exposure to Chromium III - Inhalation (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/m ³)	Serious (mg/m ³)		

Hemato 1.99

a The number corresponds to entries in Figure 3-2.

b Used to derive an intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m³ as insoluble trivalent chromium particulates. The minimal LOAEL of 3 mg chromium(III)/m³ was adjusted for intermittent exposure, converted to a human equivalent concentration (0.43 mg chromium(III)/m³), and divided by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability).

c Used to derive an intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m³ as soluble trivalent chromium particulates. The LOAEL of 3 mg chromium(III)/m³ was duration-adjusted for intermittent exposure, converted to a human equivalent concentration (0.04 mg chromium(III)/m³) and divided by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation

Acute (≤14 days)

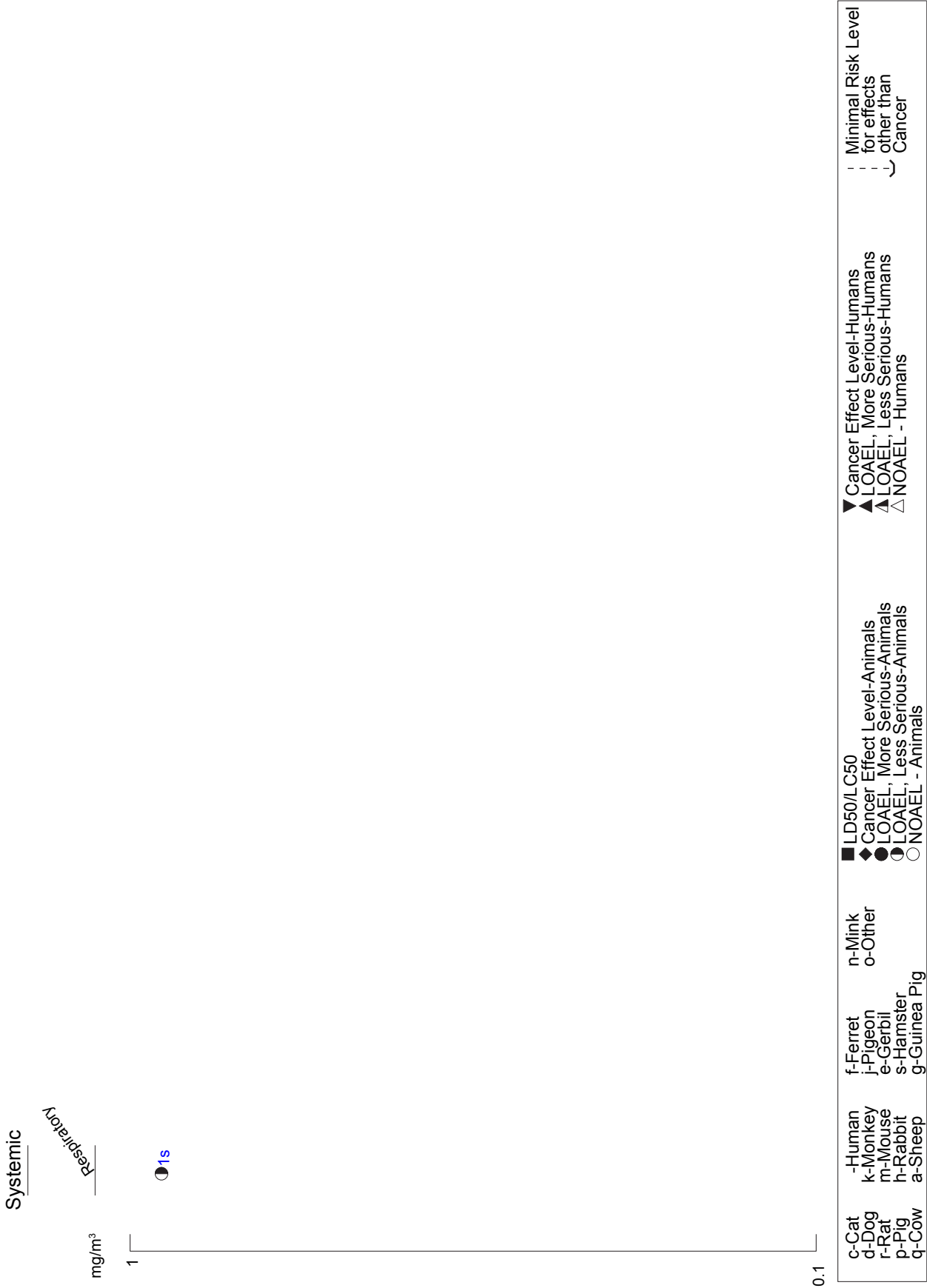


Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation (Continued)

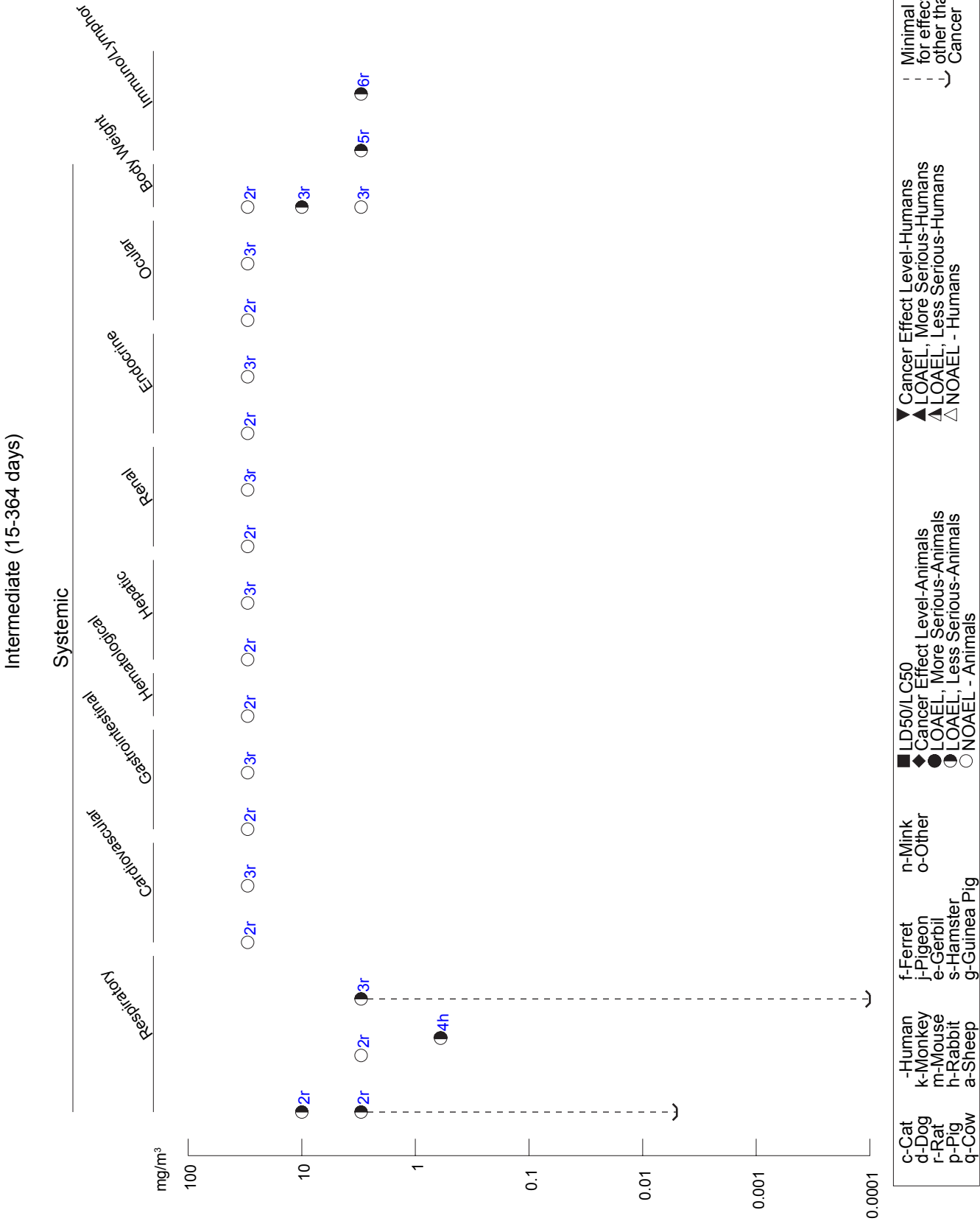
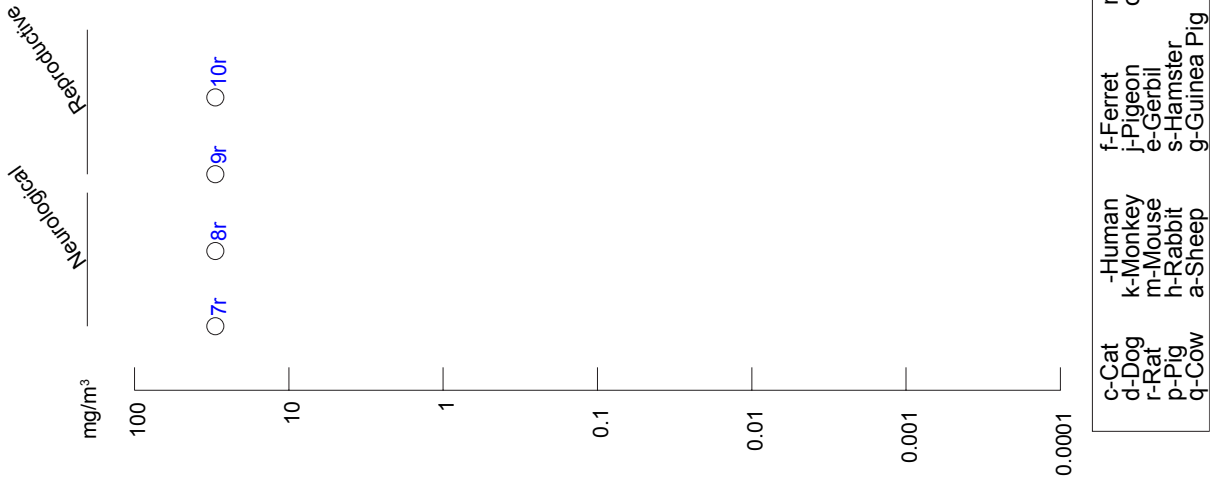


Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation (Continued)

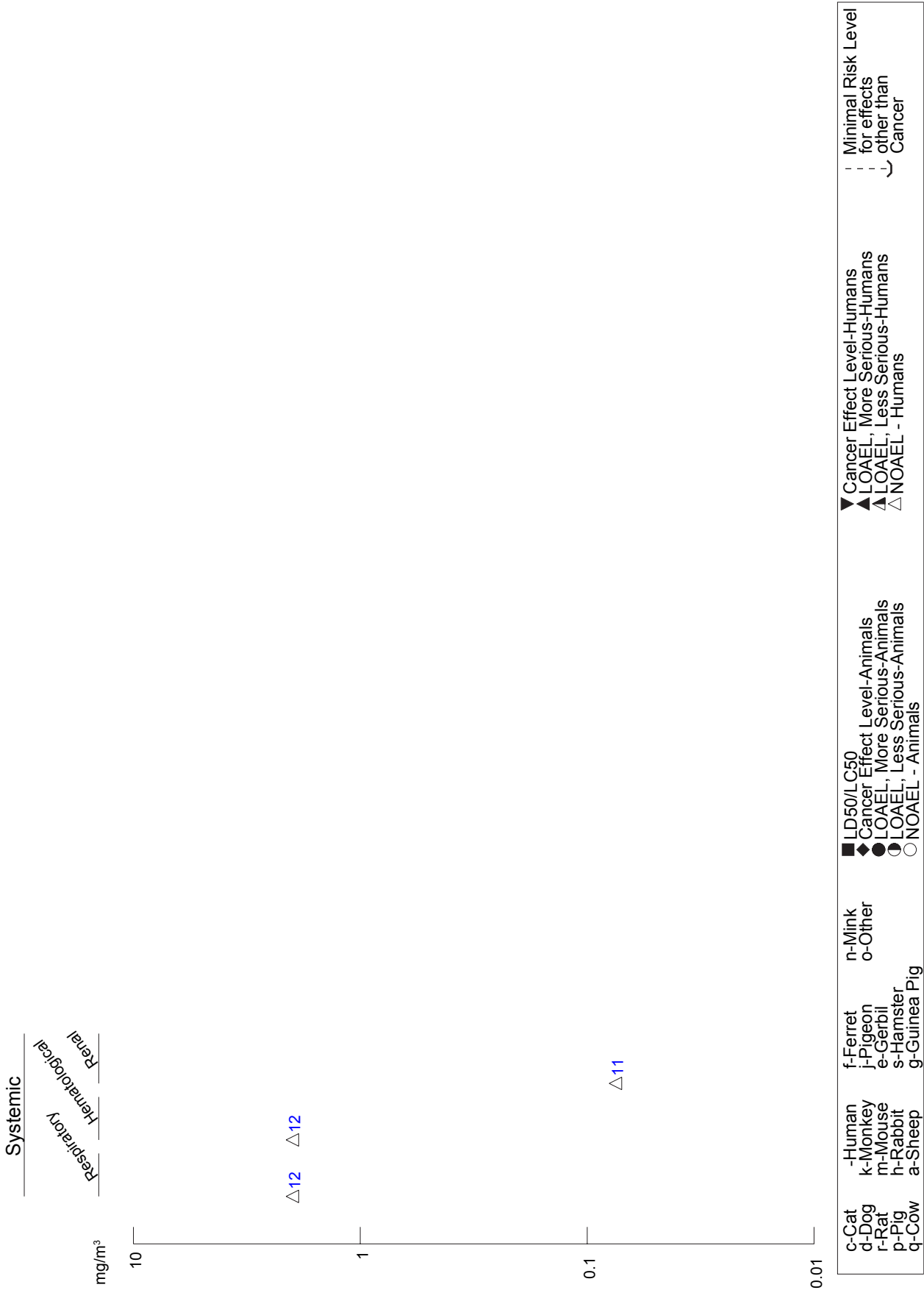
Intermediate (15-364 days)



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Figure 3-2 Levels of Significant Exposure to Chromium III - Inhalation (Continued)

Chronic (≥365 days)



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perforation was found in both subjects upon physical examination (Meyers 1950). In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of sneezing, rhinorrhea, labored breathing, and a choking sensation when they were working over the chromate tanks. All five of the subjects had thick nasal and postnasal discharge and nasal septum ulceration or perforation after 2–3 months of exposure (Lieberman 1941). Asthma developed in a man who had been well until 1 week after beginning employment as an electroplater. When challenged with an inhalation exposure to a sample of chromium(III) sulfate, he developed coughing, wheezing, and decreased forced expiratory volume. He also had a strong asthmatic reaction to nickel sulfate (Novey et al. 1983). Thus, chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high.

Intermediate- to chronic-duration occupational exposure to chromium(VI) may cause an increased risk of death due to noncancer respiratory disease. In a retrospective mortality study of 1,288 male and 1,401 female workers employed for at least 6 months in a chrome plating and metal engineering plant in the United Kingdom between 1946 and 1975, a statistically significant excess of death from diseases of the respiratory system (noncancer) were obtained for men (observed/expected [O/E]=72/54.8, standard mortality ratio [SMR]=131, $p<0.05$) and men and women combined (O/E=97/76.4, SMR=127, $p<0.05$), but not for women alone. Exposure was mainly to chromium trioxide, but exposure concentrations were not precisely known. The contribution of nickel exposure to the effects was found to be unimportant, while data on smoking habits were not available (Sorahan et al. 1987). Similarly, a high SMR was found for noncancer respiratory disease among 1,212 male chromate workers who were employed for at least 3 months in three chromate plants in the United States during the years 1937–1960 and followed for 24 years (O/E=19/7.843, SMR=242) (Taylor 1966). The increased risk of death from respiratory effects correlated with duration of employment in chromate production, but no information on exposure levels, smoking habits, or exposure to other chemicals was provided. The nature of the respiratory diseases was not further described in either of these reports. Chromate production workers in the United Kingdom who were first employed before 1945 had a high risk of death from chronic obstructive airways disease (O/E=41/28.66, SMR=143, $p<0.05$) (Davies et al. 1991). Exposure concentrations were not known, and reliable smoking data were not available.

Occupational exposure to chromium(VI) as chromium trioxide in the electroplating industry caused upper respiratory problems. A case history of nine men in a chrome plating facility reported seven cases of nasal septum ulceration. Signs and symptoms included rhinorrhea, nasal itching and soreness, and

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epistaxis. The men were exposed from 0.5 to 12 months to chromium trioxide at concentrations ranging from 0.09 to 0.73 mg chromium(VI)/m³ (Kleinfeld and Rosso 1965). Electroplating workers in Sao Paulo, Brazil, exposed to chromium trioxide vapors while working with hot chromium trioxide solutions had frequent incidences of coughing, expectoration, nasal irritation, sneezing, rhinorrhea, and nose-bleed and developed nasal septum ulceration and perforation. The workers had been employed for <1 year, and most of the workers had been exposed to concentrations >0.1 mg chromium(VI)/m³ (Gomes 1972). Nose and throat irritation, rhinorrhea, and nose-bleed also occurred at higher incidence in chrome platers in Singapore than in controls (Lee and Goh 1988).

Numerous studies of workers chronically exposed to chromium(VI) compounds have reported nasal septum perforation and other respiratory effects. Workers at an electroplating facility exposed to 0.0001–0.0071 mg chromium(VI)/m³ as chromium trioxide for an average of 26.9 months complained of excessive sneezing, rhinorrhea, and epistaxis. Many of the workers had ulcerations and/or perforations of the nasal mucosa (Cohen et al. 1974). A study using only questionnaires, which were completed by 997 chrome platers and 1,117 controls, found a statistically significant increase in the incidence of chronic rhinitis, rhinitis with bronchitis, and nasal ulcers and perforations in workers exposed to chromium(VI) in the chrome plating industry in 54 plants compared to the control population (Royle 1975b). The workers had been exposed to chromium(VI) in air and in dust. The air levels were generally <0.03 mg chromium(VI)/m³, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g. The exposure levels at which effects first occurred could not be determined. A NIOSH Health Hazard Evaluation of an electroplating facility in the United States reported nasal septum perforation in 4 of 11 workers employed for an average of 7.5 years and exposed to mean concentrations of 0.004 mg chromium(VI)/m³. Many of the workers had epistaxis, rhinitis, and nasal ulceration (Lucas and Kramkowski 1975). Nasal mucosal changes ranging from irritation to perforation of the septum were found among 77 employees of eight chromium electroplating facilities in Czechoslovakia where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m³ (Hanslian et al. 1967). The incidence of olfactory cleft obstruction, dry nose, feelings of nasal obstruction, and nasal crusting was significantly increased in workers employed at chromium plating factories (mean employment duration of 7.9 years) in An-San, Korea compared to an unexposed control group (Kitamura et al. 2003). Air concentrations of chromium(VI) ranged from 0.005 to 0.03 mg chromium(VI)/m³ and of chromium(III) ranged from 0.005 to 0.06 mg chromium(III)/m³. Increased incidences of nasal septum perforation, nasal septum ulcer, and nasal obstruction were observed in workers at chromium electroplating facilities exposed for a mean duration of 6.1 years, as compared to workers at zinc electroplating facilities (Kuo et al. 1997a). The chromium electroplating workers had 31.7 and 43.9 times

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greater risks of developing nasal septum ulcers or nasal perforations, respectively, than the zinc workers. A significant relationship between duration of exposure and the risk of nasal septum ulcers was also found; the chromium electroplating workers with a work duration of >9 years had a risk 30.8 times higher than those with a work duration of <2 years. Duration did not significantly affect the risk of nasal perforation. Statistically significant decreases in vital capacity, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV₁) were also observed in the chromium workers. Alterations in lung function were also reported in a study of 44 workers at 17 chromium electroplating facilities (Bovet et al. 1977). Statistically significant decreases in forced expiratory volume in 1 second and forced expiratory flow were observed; vital capacity was not altered. Lower lung function values were found among workers with high urinary chromium levels (exposure levels were not reported), and it was determined that cigarette smoking was not a confounding variable.

A study of respiratory effects, lung function, and changes in the nasal mucosa in 43 chrome plating workers in Sweden exposed to chromium(VI) as chromium trioxide for 0.2–23.6 years (median=2.5 years) reported respiratory effects at occupational exposure levels of 0.002 mg chromium(VI)/m³. Signs and symptoms of adverse nasal effects were observed and reported at mean exposure levels of 0.002–0.2 mg chromium(VI)/m³. Effects noted at ≤0.002 mg chromium(VI)/m³ included a smeary and crusty septal mucosa and atrophied mucosa. Nasal mucosal ulceration and septal perforation occurred in individuals exposed at peak levels of 0.02–0.046 mg chromium(VI)/m³; nasal mucosal atrophy and irritation occurred in individuals exposed at peak levels of 0.0025–0.011 mg chromium(VI)/m³; and no significant nasal effects were observed in individuals exposed at peak levels of 0.0002–0.001 mg chromium(VI)/m³. Workers exposed to mean concentrations of 0.002–0.02 mg chromium(VI)/m³ had slight, transient decreases in FVC, forced expired volume in 1 second (FEV₁), and forced mid-expiratory flow during the workday. Workers exposed to <0.002 mg chromium(VI)/m³ showed no effects on lung function (Lindberg and Hedenstierna 1983). The concentrations at which minor lung function changes were observed (0.002–0.02 mg chromium(VI)/m³) and those at which no changes were observed (<0.002 mg chromium(VI)/m³) are similar to those for nasal effects (0.0025–0.011 mg chromium(VI)/m³). The effects observed in this study may not have resulted from exposure levels actually measured, but may have resulted from earlier exposure under unknown conditions. Furthermore, poor personal hygiene practices resulting in transfer of chromium(VI) in chrome plating solutions from the hands to the nose could contribute to the development of nasal ulceration and perforation (Cohen et al. 1974; Lucas and Kramkowski 1975), perhaps leading to an underestimation of airborne levels of chromium(VI) necessary to cause these effects. Despite these considerations, the study by Lindberg and Hedenstierna (1983) is useful because it indicates concentration-responses of

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chromium(VI) compounds that cause significant nasal and respiratory effects. The LOAEL of 0.002 mg chromium(VI)/m³ for respiratory effects in humans was used to calculate an inhalation MRL of 5×10^{-6} mg chromium(VI)/m³ for intermediate-duration exposure to chromium(VI) as chromium trioxide mists and other dissolved hexavalent chromium aerosols or mists as described in the footnotes in [Table 3-1](#).

Occupational exposure to chromium(VI) and/or chromium(III) in other chromium-related industries has also been associated with respiratory effects. These industries include chromate and dichromate production, stainless steel welding, and possibly ferrochromium production and chromite mining.

In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥ 0.01 mg chromium(VI)/m³, high incidences of nasal septum perforation, septal atrophy and ulcerations, sinusitis, pharyngitis, and bronchitis were found among 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year (Sassi 1956). Medical records of 2,307 male workers employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). The most frequently reported clinical symptoms were irritation and ulcerated nasal septum, occurring in 68.1 and 62.9% of the cohort, respectively. For irritation of the nasal septum, the mean time of employment to first diagnosis was 89 days and the mean annual exposure level during the year of first diagnosis was 0.025 mg chromium(VI)/m³; for nasal septal ulceration, the mean time of employment to first diagnosis was 86 days and the mean annual exposure level during the year of first diagnosis was 0.028 mg chromium(VI)/m³. Other nasal effects had a longer time to first diagnosis. The time to first diagnosis for perforated nasal septum was 313 days, occurring in 17.3% of the cohort at a mean exposure level of 0.033 mg chromium(VI)/m³, and for bleeding nasal septum, the time to first diagnosis was 418 days, occurring in 12.1% of the cohort at a mean exposure level of 0.025 mg chromium(VI)/m³. In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, evaluation for respiratory effects revealed that 63% had perforations of the nasal septum, 86.6% had chemical rhinitis, 42.3% had chronic chemical pharyngitis, 10.35% had laryngitis, and 12.1% had sinus, nasal, or laryngeal polyps. The number of complaints and clinical signs increased as the exposure to respirable chromium(VI) and chromium(III) compounds increased, but exposure levels at which effects first occurred were not clearly defined (Mancuso 1951). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found that effects on the lungs

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consisted of bilateral hilar enlargement. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m³); water-soluble hexavalent chromium compounds (0.005–0.17 mg chromium(VI)/m³); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m³) (PHS 1953). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases (Keskinen et al. 1980). In a study of 54 male miners in Zimbabwe exposed to chrome ore dust, decreases in pulmonary function, as indicated by measures of FVC, FEV₁, peak expiratory flow rate (PEFR), and FEV₁%, was observed compared to an unexposed control (e.g., non-mining) population (Osim et al. 1999). Exposure levels were reported only as respirable dust, not as chromium specifically, and the mining company did not employ industrial hygiene practices to reduce exposure. In this same study, no changes in lung function were observed in a group of 46 male miners working for a company following industrial hygiene procedures (again, specific chromium exposure levels were not reported). The analysis controlled for smoking and infectious respiratory diseases. In a report of 10 cases of pneumoconiosis in underground workers in chromite mines in South Africa, radiographic analysis revealed fine nodulation and hilar shadows. Chromium in the chromite ore in South Africa was in the form of chromium(III) oxide. The cause of the pneumoconiosis was considered to be deposition of insoluble radio-opaque chromite dust in the tissues, rather than fibrosis (Sluis-Cremer and du Toit 1968). In a case report of a death of a sandblaster in a ferrochromium department of an iron works, the cause of death was silicosis, but autopsy also revealed diffuse enlargement of alveolar septae and chemical interstitial and alveolar chronic pneumonia, which were attributed to inhalation of chromium(III) oxide (Letterer 1939). In an industrial hygiene survey of 60 ferrochromium workers exposed to chromium(III) and chromium(VI) (0.02–0.19 mg total chromium/m³) conducted in 1975, appreciably higher incidences of subjective symptoms of coughing, wheezing, and dyspnea were reported compared with controls. These workers had been employed at the plant for at least 15 years. The control group consisted of workers employed at the same plant for <5 years. Statistically significant decreased mean FVC (p<0.01) and FEV₁ (p<0.05) were found in the ferrochromium workers compared with controls. Two of the ferrochromium workers had nasal septum perforations, which were attributed to previous exposure to hexavalent chromium. A major limitation of this study is that the control group was significantly younger than the study cohort. In addition, the weekly amount of tobacco smoked by the control group was slightly greater than that smoked by the study groups, and the controls began smoking 5 years earlier than the study groups. Therefore, the increase in subjective respiratory symptoms and decreased pulmonary function parameters cannot unequivocally be attributed to chromium exposure (Langård 1980). However, no increase in the

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prevalence of respiratory illness was found in a study of 128 workers from two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b) or in 106 workers at a factory that produced these chromium(III) compounds where workroom levels were ≤ 1.99 mg chromium(III)/m³ (Korallus et al. 1974a). Similar results were reported in a cross-sectional study that was conducted to determine whether occupational exposure to trivalent chromium or hexavalent chromium caused respiratory diseases, decreases in pulmonary function, or signs of pneumoconiosis in stainless steel production workers (Huvinen et al. 1996). The median personal exposure levels were 0.0005 $\mu\text{g}/\text{m}^3$ for chromium(VI) and 0.022 $\mu\text{g}/\text{m}^3$ for chromium(III); the 221 workers were employed for >8 years with an average potential exposure of 18 years. Spirometry measurements were taken and chest radiographic examinations were conducted. There were no significant differences in the odds ratios between the exposed workers and the 95 workers in the control group. The deficits in lung function shown in both populations could be explained by age and smoking habits. In a follow-up study of these workers (Huvinen et al. 2002a), no adverse respiratory effects were observed (as assessed by spirometry, chest x-ray, and self-reported symptoms) in workers in the chromium(VI) group (n=104) compared to controls (n=81). Workers exposed to chromium(III) in the sintering and crushing departments (n=68) reported an increase in respiratory symptoms (phlegm production, shortness of breath on exertion) compared to control, but no differences in spirometry or chest x-ray. Workers exposed to chromium(III) as chromite ore (n=31) had lower lung function tests, although smoking was a confounding factor. In addition to chromium, workers were also exposed to nickel and molybdenum. In a study of stainless steel workers (all nonsmokers) exposed for a minimum of 14 years to chromium(VI) (n=29), chromium(III) (n=14), or chromite(III) ore (n=5), no increase was observed in the incidence of nasal diseases or nasal symptoms in chromium-exposed workers compared to a control population of 39 workers (Huvinen et al. 2002b). However, although an exposure-related increase in the incidence of clinical signs of nasal irritation was not observed, anterior rhinoscopy revealed a slight increase in the incidence of inflammatory changes in the nasal mucosa of workers exposed to chromium(VI) (risk ratio=2.4) or chromium(III) (risk ratio=2.3), compared to control. The mean exposure level for the chromium(VI) group was 0.5 $\mu\text{g Cr(VI)}/\text{m}^3$, for the chromium(III) group was 248 $\mu\text{g total Cr}/\text{m}^3$ (concentration of chromium(III) not reported) and for the chromite ore group was 22 $\mu\text{g Cr(III)}/\text{m}^3$.

The respiratory system in animals is also a primary target for acute- and intermediate-duration inhalation exposure to chromium(VI) and chromium(III). Rats exposed to sodium dichromate for 28 or 90 days had increased lung weight but no histopathological abnormalities at concentrations ≤ 0.2 mg chromium(VI)/m³. The percentage of lymphocytes was increased in the bronchoalveolar lavage fluid at ≥ 0.025 mg/m³. A decrease in macrophage activity was observed in the 0.2 mg chromium(VI)/m³ group

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exposed for 90 days. Clearance of iron oxide from the lungs decreased in rats exposed to 0.2 mg chromium(VI)/m³ for 42 days prior to and 49 days after challenge with iron oxide particles when compared to controls. The decreased clearance of iron oxide correlated with the decrease in macrophage activity (Glaser et al. 1985). In a similar but more extensive study, obstructive respiratory dyspnea was observed in rats exposed to sodium dichromate at ≥ 0.2 mg chromium(VI)/m³ for 30 or 90 days, and mean lung weight was increased at ≥ 0.05 mg chromium(VI)/m³. Slight hyperplasia was observed at high incidence in rats at ≥ 0.05 mg chromium(VI)/m³. Lung fibrosis occurred at low incidence in the rats exposed to ≥ 0.1 mg chromium(VI)/m³ for 30 days, but not in the 0.05 mg/m³ or the control groups. The incidence of both these lesions declined after longer exposure, indicating repair. Accumulation of macrophages and inflammation occurred at ≥ 0.05 mg chromium(VI)/m³ regardless of duration. Results of bronchoalveolar lavage (BAL) analysis provided further evidence of an irritation effect that was reversible (Glaser et al. 1990). The data from the Glaser et al. (1990) study was used to develop benchmark concentrations (BMCs) (Malsch et al. 1994). The BMC of 0.016 mg chromium(VI)/m³ for alterations in lactate dehydrogenase levels in BAL fluid was used to calculate an inhalation MRL of 0.0003 mg chromium(VI)/m³ for intermediate-duration exposure to chromium(VI) as particulate hexavalent compounds as described in the footnote of [Table 3-1](#).

Male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m³ as chromium trioxide mist developed nasal hemorrhage after 10 days (lasting for 4 weeks) during a 90-day inhalation study (Kim et al. 2004). "Peculiar sounds" during respiration were noted starting after 1 week of exposure and resolving by week 8 in rats exposed to ≥ 0.23 mg chromium(VI)/m³; however, no additional information on this observation was reported. After 90 days, histopathological changes to respiratory tissue included macrophage aggregation and foamy cells, and inflammation of alveolar regions; however, no abnormalities were observed in nasal tissue at 0.49 mg chromium(VI)/m³ (incidence data were not reported). Mice exposed to chromium trioxide mist at concentrations of 1.81 and 3.63 mg chromium(VI)/m³ intermittently for ≤ 12 months developed perforations in the nasal septum, hyperplastic and metaplastic changes in the larynx, trachea, and bronchus, and emphysema (Adachi 1987; Adachi et al. 1986).

The respiratory effects of chromium(III) compounds were investigated in male and female CDF rats exposed to insoluble chromic oxide or soluble basic chromium sulfate by nose-only inhalation at 3, 10, or 30 mg chromium(III)/m³ for 6 hours/day, 5 days/week for 13 weeks (Derelanko et al. 1999). After 5 days of exposure, BAL was conducted on a subgroup of animals. In rats treated with chromic oxide, a yellow crystalline material was observed in the cytoplasm of mononuclear cells of all exposure groups; however,

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it is not clear if this observation represents an adverse effect. No other BAL parameters were affected (nucleated cell count and differential, protein and BAL fluid activities of β -glucuronidase, lactic dehydrogenase, and glutathione reductase). In rats treated with basic chromium sulfate, BAL fluid analysis showed significant decreases in nucleated cells at all doses in males and females and decreases in the percentage of segmented neutrophils and mononuclear cells at 30 mg chromium(III)/m³ in males. Increased amounts of cell debris and lysed cells were present in all basic chromium sulfate groups (incidence data were not reported). In rats exposed to chromic oxide for 13 weeks, absolute and relative lung weights were increased by 12 and 13%, respectively, in males exposed to 30 mg chromium(III)/m³ as chromic oxide; no change was observed in females. Histopathological examination of respiratory tissues showed pigmented macrophages containing a dense black substance, presumably the test substance, throughout the terminal bronchioles and alveolar spaces in rats from all treatment groups; this finding is consistent with normal physiological clearance mechanisms for particulates deposited in the lung and is not considered to be adverse. At concentrations of 10 and 30 mg chromium(III)/m³, trace to mild chronic interstitial inflammation, characterized by inflammatory cell infiltrates, and septal cell hyperplasia was observed. No lesions were observed in the nasal cavity. Following a 13-week recovery period, microscopic examination of respiratory tissues of rats treated with chromic oxide showed pigmented macrophages and black pigment in peribronchial tissues and the mediastinal lymph node in all treatment groups and septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m³. In rats treated with basic chromium sulfate, a dose-related increase in absolute and relative lungs weights was observed in all treatment groups. Histopathological examination of respiratory tract tissues revealed chronic inflammation of the lung (characterized by cell infiltration and debris in alveolar spaces and intense inflammation) and alveolar wall hyperplasia in all treatment groups. In addition, inflammation and suppurative and mucoid exudates of nasal tissues and granulomatous inflammation of the larynx were observed in all treatment groups. Incidence data for histopathological findings were not reported. Following the 13-week recovery period for rats treated with basic chromium sulfate, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m³ groups, nasal tissues (trace suppurative exudates) in one to two animals in each group, and mediastinal lymph node (histiocytosis and hyperplasia) in all chromium(III) exposed groups. Results of this study demonstrate differences in the respiratory effects of inhaled chromium oxide and inhaled basic chromium sulfate. Effects of soluble basic chromium sulfate were more severe and were observed throughout the

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respiratory tract, while effects of chromic oxide were more mild and limited to the lung; these observations may be related to differences in chemical-physical properties of the test compounds. Data from the Derelanko et al. (1999) study was used as the basis for intermediate-duration inhalation MRLs for chromium(III) compounds. Since soluble and insoluble chromium(III) compounds exhibited different effects in the respiratory tract, distinct intermediate-duration MRLs were derived for insoluble and soluble trivalent chromium particulates. For insoluble chromium(III) compounds (chromic oxide), the minimal LOAEL of 3 mg chromium(III)/m³ was used to calculate an intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m³ for exposure to trivalent chromium particulates as described in the footnote of Table 3-2. For soluble chromium(III) (basic chromium sulfate) compounds, the LOAEL of 3 mg chromium(III)/m³ was used to calculate an intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m³ for exposure to trivalent chromium particulates as described in the footnote of Table 3-2.

Pulmonary fluid from hamsters exposed to 0.9 or 25 mg chromium(III)/m³ as chromium trichloride for 30 minutes revealed sporadic changes in activities of acid phosphatase and alkaline phosphatase in the lavage fluid at 25 mg chromium(III)/m³. In the lung tissue, a 75% increase in the acid phosphatase activity was found at 0.9 mg chromium(III)/m³ and in the β -glucuronidase activity at an unspecified concentration. Histological examination revealed alterations representing mild nonspecific irritation but no morphological damage (Henderson et al. 1979). In rabbits exposed to 0.6 mg chromium(III)/m³ as chromium nitrate intermittently for 4–6 weeks, changes in the lungs were confined to nodular accumulations of macrophages in the lungs. Macrophage morphology demonstrated black inclusions and large lysosomes. These changes represent normal physiological responses of the macrophages to the chromium particle. Phagocytosis and the reduction of nitroblue tetrazolium to formazan was impaired by chromium(III), indicating a decrease in the functional and metabolic activity of the macrophage (Johansson et al. 1986a, 1986b).

Chronic exposure to chromium(VI) compounds and mixtures of chromium(VI) and chromium(III) compounds have also resulted in adverse respiratory effects in animals. Experiments in which rats were exposed to either chromium(VI) alone as sodium dichromate or a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months showed similar loading of macrophages and increases in lung weight. However, histopathology of rats exposed to 0.1 mg/m³ of chromium(III) and chromium(VI) together revealed interstitial fibrosis and thickening of the septa of the alveolar lumens due to the large accumulation of chromium in the lungs, whereas histopathology of the lungs was normal in rats exposed only to chromium(VI) (Glaser et al. 1986, 1988). Mice exposed to 4.3 mg chromium(VI)/m³ as calcium

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chromate dust intermittently for 18 months had epithelialization of alveoli. Histopathology revealed epithelial necrosis and marked hyperplasia of the large and medium bronchi, with numerous openings in the bronchiolar walls (Nettesheim and Szakal 1972). Significantly increased incidences of pulmonary lesions (lung abscesses, bronchopneumonia, giant cells, and granulomata) were found in rats exposed chronically to a finely ground, mixed chromium roast material that resulted in airborne concentrations of 1.6–2.1 mg chromium(VI)/m³ compared with controls. In the same study, guinea pigs exposed chronically to the chromium roast material along with mists of potassium dichromate or sodium chromate solutions that also resulted in 1.6–2.1 mg chromium(VI)/m³ had significantly increased incidences of alveolar and interstitial inflammation, alveolar hyperplasia, and interstitial fibrosis, compared with controls. Similarly, rabbits were also exposed and also had pulmonary lesions similar to those seen in the rats and guinea pigs, but the number of rabbits was too small for meaningful statistical analysis (Steffee and Baetjer 1965).

In the only study of chromium(IV) exposure, all rats treated with 0.31 or 15.5 mg chromium(IV)/m³ as chromium dioxide dust for 2 years had discolored mediastinal lymph nodes and lungs, and dust laden macrophages. Lung weight was increased at 12 and 24 months in the 15.5 mg chromium(IV)/m³ group (Lee et al. 1989). The increased lung weight and macrophage effects probably represent the increased lung burden of chromium dioxide dust and normal physiological responses of macrophages to dust.

Cardiovascular Effects. Information regarding cardiovascular effects in humans after inhalation exposure to chromium and its compounds is limited. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥ 0.01 mg chromium(VI)/m³, electrocardiograms were recorded for 22 of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year. No abnormalities were found (Sassi 1956). An extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants found no association between heart disease or effects on blood pressure and exposure to chromates. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m³); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m³); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent trivalent chromium (0–0.47 mg chromium/m³) (PHS 1953). No excess deaths were observed from cardiovascular diseases and ischemic heart disease in a cohort of 4,227 stainless steel production workers from 1968 to 1984 when compared to expected deaths based on national rates and matched for age, sex, and calendar time (Moulin et al. 1993). No measurements of exposure were provided. In a cohort of 3,408 individuals who had worked in four facilities that

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produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971, where the exposure durations of workers ranged from <1 to >20 years, and no increases in atherosclerotic heart disease were evident (Rosenman and Stanbury 1996). The proportionate mortality ratios (number of deaths from a specific cause to the total number of deaths) for white and black men were 97 (95% confidence limits 88–107) and 90 (95% confidence limits 72–111), respectively.

Cardiovascular function was studied in 230 middle-aged workers involved in potassium dichromate production who had clinical manifestations of chromium poisoning (96 with respiratory effects and 134 with gastrointestinal disorders) and in a control group of 70 healthy workers of similar age. Both groups with clinical manifestations had changes in the bioelectric and mechanical activity of the myocardium as determined by electrocardiography, kinetocardiography, rheocardiography, and ballistocardiography. These changes were more pronounced in the workers with respiratory disorders due to chromium exposure than in the workers with chromium-induced gastrointestinal effects. The changes in the myocardium could be secondary to pulmonary effects and/or to a direct effect on the blood vessels and myocardium (Kleiner et al. 1970).

For intermediate-duration exposures, no histopathological changes to the heart were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m³ as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m³ as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). No histopathological lesions were found in the hearts of rats exposed chronically to chromium dioxide at 15.5 mg chromium(IV)/m³ (Lee et al. 1989). Additional information regarding cardiovascular effects in animals after exposure to chromium or chromium compounds was not located.

Gastrointestinal Effects. Gastrointestinal effects have been associated with occupational exposure of humans to chromium compounds. In a report of two cases of acute exposure to "massive amounts" of chromium trioxide fumes, the patients complained of abdominal or substernal pain, but further characterization was not provided (Meyers 1950).

In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, 5 of 11 workers reported symptoms of stomach pain, 2 of duodenal ulcer, 1 of gastritis, 1 of stomach cramps, and 1 of frequent indigestion. The workers were employed for an average of 7.5 years and were exposed to mean concentrations of 0.004 mg chromium(VI)/m³ (Lucas and Kramkowski 1975). These workers were not compared to a control group. An otolaryngological examination of 77 employees of eight chromium

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electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was $0.414 \text{ mg chromium(VI)/m}^3$, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophy of the left larynx (Hanslian et al. 1967). In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, gastrointestinal radiography revealed that 10 of the workers had ulcer formation, and of these, 6 had hypertrophic gastritis. Nearly all of the workers breathed through the mouth while at work and swallowed the chromate dust, thereby directly exposing the gastrointestinal mucosa. Only two cases of gastrointestinal ulcer were found in 41 control individuals, who had the same racial, social, and economic characteristics as the chromium-exposed group (Mancuso 1951). In a survey of a facility engaged in chromate production in Italy where exposure concentrations were $\geq 0.01 \text{ mg chromium(VI)/m}^3$, 15.4% of the 65 workers who worked in the production of dichromate and chromium trioxide for at least 1 year had duodenal ulcers and 9.2% had colitis. The ulcers were considered to be due to exposure to chromium (Sassi 1956). Gastric mucosa irritation leading to duodenal ulcer was found in 21 of 90 workers engaged in the production of chromium salts. Symptoms of gastrointestinal pathology appeared about 3–5 years after the workers' initial contact (Sterekhova et al. 1978). Most of these studies reporting gastrointestinal effects did not compare the workers with appropriate controls. Although the gastrointestinal irritation and ulceration due to exposure to chromium(VI) in air could be due to a direct action of chromium(VI) on the gastrointestinal mucosa from swallowing chromium as a result of mouth breathing (or transfer via hand-to-mouth activity), other factors, such as stress and diet, can also cause gastrointestinal effects. While occupational exposure to chromium(VI) may result in gastrointestinal effects, a lower than expected incidence of death from diseases of the digestive tract was found among a cohort of 2,101 employees who had worked for at least 90 days during the years 1945–1959 in a chromium production plant in Baltimore, Maryland, and were followed until 1977. The rate ($O/E=23/36.16$, $SMR=64$) is based on comparison with mortality rates for Baltimore (Hayes et al. 1979). In contrast to findings with chromium(VI) compounds, no indication was found that exposure to chromium(III) resulted in stomach disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

Information regarding gastrointestinal effects in animals after inhalation exposure to chromium or its compounds is limited. For intermediate-duration exposures, no histopathological changes to gastrointestinal tissues in male and female CDF rats exposed to $30 \text{ mg chromium(III)/m}^3$ as chromic oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). Histological examination of the stomachs of rats exposed to sodium dichromate dihydrate at $\leq 0.2 \text{ mg chromium(VI)/m}^3$ for 28 or 90 days revealed no abnormalities (Glaser et al. 1985). In mice exposed intermittently to 4.3 mg

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chromium(VI)/m³ as calcium chromate for 18 months, small ulcerations in the stomach and intestinal mucosa were reported to occur occasionally, but the incidence in the treated mice or controls and other details regarding these lesions were not reported (Nettesheim et al. 1971). No treatment-related histopathological lesions were found in the stomach, large intestine, duodenum, jejunum, or ileum of rats chronically exposed to chromium dioxide at 15.5 mg chromium(IV)/m³ (Lee et al. 1989).

Hematological Effects. Hematological evaluations of workers occupationally exposed to chromium compounds have yielded equivocal results. Ninety-seven workers from a chromate plant were exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble sodium chromate and dichromate. Hematological evaluations revealed leukocytosis in 14.4% or leukopenia in 19.6% of the workers. The leukocytosis appeared to be related primarily to monocytosis and eosinophilia, but controls had slight increases in monocytes and occasional increases in eosinophils without leukocytosis. Decreases in hemoglobin concentrations and slight increases in bleeding time were also observed (Mancuso 1951). Whether these hematological findings were significantly different from those seen in controls was not stated, but the effects were attributed to chromium exposure. In a survey of a facility engaged in chromate production in Italy where exposure concentrations were ≥ 0.01 mg chromium(VI)/m³, hematological evaluation of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were unremarkable or inconclusive (Sassi 1956). In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, hematological evaluations revealed no effects on red blood cell counts, hemoglobin, hematocrit, or white blood cell counts. The sedimentation rate of red cells was higher than that of controls, but the difference was not statistically significant. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m³); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m³); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m³) (PHS 1953). Likewise, no effects on red blood cell counts, white blood cell counts, hemoglobin levels, or sedimentation rate were found in a case control study of 17 male manual metal arc stainless steel welders from six industries with mean occupational durations of 20 years (Littorin et al. 1984). The relationship between serum and urine chromium levels and blood hemoglobin was examined in workers exposed to chromium(III) at a tannery plant in Leon, Mexico (Kornhauser et al. 2002). Groups of workers were classified as unexposed (control; n=11), moderately exposed (n=14) or highly exposed (n=11) based on job type; exposure levels were not reported. Blood chromium levels of 0.13, 0.25, and 0.39 $\mu\text{g/L}$ and urine chromium levels of 1.35, 1.43, and 1.71 $\mu\text{g/L}$ were observed in the control, moderate, and high exposure groups, respectively; statistically significant

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differences were observed between the control group and both chromium groups for blood chromium and between the control and the high exposure groups for urine chromium. An inverse relationship was observed between urine chromium and blood hemoglobin ($r=-0.530$), serum chromium and urine iron ($r=-0.375$) and the chromium/iron ratio in urine and hemoglobin ($r=-0.669$; <0.05). Results indicate a potential effect of chromium(III) exposure on hemoglobin; however, due to small group size, definitive conclusions cannot be made. No hematological disorders were found among 106 workers in a chromium(III) producing plant where workroom levels were ≤ 1.99 mg chromium(III)/m³ as chromium(III) oxide and chromium(III) sulfate (Korallus et al. 1974a).

Results from hematological evaluations in rats yielded conflicting results. Hematological effects were observed in male Sprague-Dawley rats exposed to chromium trioxide mist for 90 days; changes included significant decreases in hematocrit (at 0.23 and 1.15, but not 0.49 mg chromium(VI)/m³), hemoglobin (at 0.49 and 1.15 mg chromium(VI)/m³) and erythrocyte count (at 1.15 mg chromium(VI)/m³) (Kim et al. 2004). Hematological evaluations of rats exposed to sodium dichromate at 0.025–0.2 mg chromium(VI)/m³ for 28 or 90 days or 0.1 mg chromium(VI)/m³ for 18 months were unremarkable (Glaser et al. 1985, 1986, 1988). However, increased white blood cell counts were found in rats exposed to ≥ 0.1 mg chromium(VI)/m³ as sodium dichromate for 30 days and at ≥ 0.05 mg chromium(VI)/m³ for 90 days. The white blood cell counts were not increased 30 days postexposure (Glaser et al. 1990). Rats exposed to 0.1 mg chromium/m³ as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months had increased red and white blood cell counts, hemoglobin content, and hematocrit (Glaser et al. 1986, 1988).

No changes in hematological parameters were observed in rats exposed to 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years (Lee et al. 1989).

In male and female CDF rats exposed to insoluble chromic oxide or soluble basic chromium sulfate by nose-only inhalation at 3, 10, or 30 mg chromium(III)/m³ for 6 hours/day, 5 days/week for 13 weeks, no adverse effects on hematological parameters were observed (Derelanko et al. 1999).

Musculoskeletal Effects. No musculoskeletal effects have been reported in either humans or animals after inhalation exposure to chromium.

Hepatic Effects. Chromium(VI) has been reported to cause severe liver effects in four of five workers exposed to chromium trioxide in the chrome plating industry. Derangement of the cells in the liver,

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necrosis, lymphocytic and histiocytic infiltration, and increases in Kupffer cells were reported. Abnormalities in tests for hepatic dysfunction included increases in sulfobromophthalein retention, gamma globulin, icterus, cephalin cholesterol flocculation, and thymol turbidity (Pascale et al. 1952). In a cohort of 4,227 workers involved in production of stainless steel from 1968 to 1984, excess deaths were observed from cirrhosis of the liver compared to expected deaths (O/E=55/31.6) based on national rates and matched for age, sex, and calendar time having an SMR of 174 with confidence limits of 131–226 (Moulin et al. 1993). No measurements of exposure were provided. Based on limited information, however, the production of chromium compounds does not appear to be associated with liver effects. As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds (84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of liver function tests 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981). In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥ 0.01 mg chromium(VI)/m³, 15 of 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year had hepatobiliary disorders. When the workers were given liver function tests, slight impairment was found in a few cases. These disorders could have been due to a variety of factors, especially heavy alcohol use (Sassi 1956). No indication was found that exposure to chromium(III) resulted in liver disorders in workers employed in two factories that produced chromium(III) oxide or chromium(III) sulfate (Korallus et al. 1974b).

The hepatic effects observed in animals after inhalation exposure to chromium or its compounds were minimal and not considered to be adverse. Rats exposed to as much as 0.4 mg chromium(VI)/m³ as sodium dichromate for ≤ 90 days did not have increased serum levels of alanine aminotransferase or alkaline phosphatase, cholesterol, creatinine, urea, or bilirubin (Glaser et al. 1990). Triglycerides and phospholipids were increased only in the 0.2 mg chromium(VI)/m³ group exposed for 90 days (Glaser et al. 1985). No histopathological changes to the liver were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m³ as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to 30 mg chromium(III)/m³ as chromic oxide or basic chromium sulfate for 3 months, (Derelanko et al. 1999). Chronic exposure of rats to 0.1 mg chromium(VI)/m³ as sodium dichromate, to 0.1 mg total chromium/m³ as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide, or to 15.5 mg chromium(IV)/m³ as chromium dioxide did not cause adverse hepatic effects as assessed by histological examination and liver function tests (Glaser et al. 1986, 1988; Lee et al. 1989).

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Renal Effects. No increases in genital/urinary disease were evident in a cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey sometime between 1937 and 1971. The proportionate mortality ratios for white and black men were 71 (40–117) and 47 (15–111), respectively. Exposure durations ranged from <1 to >20 years (Rosenman and Stanbury 1996).

Renal function has been studied in workers engaged in chromate and dichromate production, in chrome platers, in stainless steel welders, in workers employed in ferrochromium production, in boilermakers, and in workers in an alloy steel plant. Workers exposed to chromium(VI) compounds in a chromate production plant were found to have higher levels of a brush border protein antigen and retinol binding protein in the urine compared with controls (Mutti et al. 1985a). A similar study was conducted in 43 male workers in the chromate and dichromate production industry, where occupational exposures were between 0.05 and 1.0 mg chromium(VI)/m³ as chromium trioxide, and mean employment duration was 7 years. Workers with >15 µg chromium/g creatinine in the urine had increased levels of retinol binding protein and tubular antigens in the urine (Franchini and Mutti 1988). These investigators believe that the presence of low molecular weight proteins like retinol binding protein or antigens in the urine are believed to be early indicators of kidney damage. In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, analysis of the urine revealed a higher frequency of white blood cell and red blood cell casts than is usually found in an industrial population (statistical significance not reported). Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m³); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m³); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m³) (PHS 1953). Significant increases in urinary N-acetyl-β-D-glucosaminidase activity and microalbumin and β₂-microglobulin levels were observed in chromate production workers (Wang et al. 2011a). The mean chromium level in air was 27.13 µg chromium/m³ and the mean exposure time was 12.86 years; however, no information on the specific chromium compound was provided. Although the workers were required to wear masks, significant correlations between air chromium levels and urinary chromium levels were found; the mean urinary chromium level was 17.41 µg/g creatinine. The study also found significant correlations between air, whole blood, and urinary chromium levels and biomarkers of renal damage (urinary N-acetyl-β-D-glucosaminidase activity and microalbumin and β₂-microglobulin levels).

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Some studies of renal function in chromate production workers found negative or equivocal results. In a survey of a facility engaged in chromate production in Italy, where exposure concentrations were ≥ 0.01 mg chromium(VI)/m³, results of periodic urinalyses of workers who worked in the production of dichromate and chromium trioxide for at least 1 year were generally unremarkable, with the exception of one case of occasional albuminuria and a few cases of slight urobilinuria (Sassi 1956). As part of a mortality and morbidity study of workers engaged in the manufacture of chromium(VI) compounds (84%) and chromium(III) compounds (16%) derived from chromium(VI) in Japan, 94 workers who had been exposed for 1–28 years were given a complete series of kidney function tests (not further characterized) 3 years after exposure ended. All values were within normal limits (Satoh et al. 1981).

Studies of renal function in chrome platers, whose exposure is mainly to chromium(VI) compounds, have also yielded equivocal results. A positive dose-response for elevated urinary levels of β_2 -microglobulin was found in chrome platers who were exposed to 0.004 mg chromium(VI)/m³, measured by personal air samplers, for a mean of 5.3 years. However, since no increase in β_2 -microglobulin levels was found in ex-chrome platers who had worked for at least 1 year in an old chrome plating plant from 1940 to 1968, this effect may be reversible (Lindberg and Vesterberg 1983b). Liu et al. (1998) similarly found significantly higher urinary β_2 -microglobulin and N-acetyl- β -glucosaminidase levels in hard-chrome electroplaters exposed to 0.0042 mg chromium/m³ for a mean of 5.8 years, as compared to aluminum anode-oxidation workers. The prevalence of elevated levels (higher than reference values) was significantly increased for N-acetyl- β -glucosaminidase, but not for β_2 -microglobulin. In another study, comparison of results of renal function tests between chrome platers and construction workers revealed that the chrome platers had significantly ($p < 0.001$) increased levels of urinary chromium and increased clearance of chromium, but decreased ($p < 0.05$) levels of retinol binding protein. However, no differences were found for blood urea nitrogen, serum and urinary β_2 -microglobulin, serum immunoglobulin, total protein in the urine, urinary albumin, N-acetyl- β -D-glucosamidase, β -galactosidase, or lysozyme (Verschoor et al. 1988).

Studies of renal function in stainless steel welders, whose exposure is mainly to chromium(VI) compounds, were negative. Stainless steel welders had significantly increased ($p < 0.001$) levels of urinary chromium, increased clearance of chromium, and increased serum creatinine compared with controls, but no differences were found in the levels of retinol binding protein, β_2 -microglobulin, or other indices of kidney damage (Verschoor et al. 1988). Similar negative results were found in another group of stainless steel welders (Littorin et al. 1984).

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Occupational exposure to chromium(III) or chromium(0) does not appear to be associated with renal effects. No renal impairment based on urinary albumin, retinol binding protein, and renal tubular antigens was found in 236 workers employed in the ferrochromium production industry where ferrochromite is reduced with coke, bauxite, and quartzite. The mean airborne concentration of chromium in various sample locations was 0.075 mg chromium(III)/m³; chromium(VI) was below the detection limit of 0.001 mg chromium(VI)/m³ at all locations (Foa et al. 1988). Workers employed in an alloy steel plant with a mean exposure of 7 years to metallic chromium at 0.61 mg chromium(0)/m³ and to other metals had normal urinary levels of total protein and β_2 -microglobulin, enzyme activities of alanine-aminopeptidase, N-acetyl- β -D-glucosaminidase, gammaglutamyl-transpeptidase, and β -galactosidase (Triebig et al. 1987). In boilermakers exposed to chromium(0), no increase in urinary levels of chromium, and no differences in the levels of retinol binding protein, β_2 -microglobulin, or other indices of renal toxicity were found (Verschoor et al. 1988).

In a group of 30 men and 25 women who were lifetime residents of an area in northern New Jersey contaminated with chromium landfill, signs of preclinical renal damage were assessed by examining the urinary levels of four proteins, intestinal alkaline phosphatase, tissue nonspecific alkaline phosphatase, N-acetyl- β -D-glucosaminidase, and microalbumin (Wedeen et al. 1996). The mean urinary chromium concentrations were 0.2 \pm 0.1 μ g/g creatinine for the women and 0.3 μ g/g creatinine for the men. None of the four proteins exceeded normal urinary levels in either men or women. The authors concluded that long-term environmental exposure to chromium dust did not lead to tubular proteinuria or signs of preclinical renal damage.

Exposure of rats to sodium dichromate at \leq 0.4 mg chromium(VI)/m³ for \leq 90 days did not cause abnormalities, as indicated by histopathological examination of the kidneys. Serum levels of creatinine and urea and urine levels of protein were also normal (Glaser et al. 1985, 1990). No changes in urinalysis parameters or histopathological changes to the kidneys were observed in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m³ as chromium trioxide (Kim et al. 2004) and no histopathological lesions were observed in the kidneys of male and female CDF rats exposed to 30 mg chromium(III)/m³ as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). Furthermore, no renal effects were observed in rats exposed to 0.1 mg chromium/m³ as sodium dichromate (chromium(VI)) or as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months, based on histological examination of the kidneys, urinalysis, and blood chemistry (Glaser et al. 1986, 1988). Rats exposed to 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years showed no histological evidence of kidney

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damage or impairment of kidney function, as measured by routine urinalysis. Serum levels of blood urea nitrogen, creatinine, and bilirubin were also normal (Lee et al. 1989).

Endocrine Effects. Increased serum amylase activity (a marker for pancreatic function) was observed in a group of 50 chrome plating workers in Bangalore, India, compared to 50 workers with no history of chromium(VI) exposure. Employment duration of exposed workers ranged from 15 to 20 years; exposure levels were not reported (Kalahasthi et al. 2007). Serum amylase activity in exposed workers was significantly correlated to urine chromium ($r=0.289$; $p<0.05$). No studies were located regarding endocrine effects in humans following inhalation exposure to chromium(III) compounds.

For intermediate-duration exposures, no histopathological changes to the endocrine tissues were observed in male Sprague-Dawley rats exposed to $1.15 \text{ mg chromium(VI)/m}^3$ as chromium trioxide (Kim et al. 2004) or in male and female CDF rats exposed to $30 \text{ mg chromium(III)/m}^3$ as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999). Male rats exposed 22 hours/day for 18 months to $0.1 \text{ mg chromium(VI)/m}^3$ as sodium dichromate or exposed to a mixture of chromium(VI) and chromium(III) ($0.06 \text{ mg chromium(VI)/m}^3$ plus $0.04 \text{ mg chromium(III)/m}^3$) as chromium(VI) trioxide and chromium(III) oxide did not result in any histopathological changes in adrenal glands (Glaser et al. 1986, 1988). Rats exposed to $15.5 \text{ mg chromium(IV)/m}^3$ as chromium dioxide for 2 years showed no histopathological abnormalities in adrenals, pancreas, and thyroid glands (Lee et al. 1989).

Dermal Effects. Acute systemic and dermal allergic reactions have been observed in chromium-sensitive individuals exposed to chromium via inhalation as described in Sections 3.2.3.2 and 3.2.3.3.

No studies were located regarding systemic dermal effects in animals after inhalation exposure to chromium(VI) or chromium(III) compounds.

Ocular Effects. Effects on the eyes due to direct contact of the eyes with airborne mists, dusts, or aerosols or chromium compounds are described in Section 3.2.3.2. Medical records of 2,307 male workers employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). Conjunctivitis was reported on 20.0% of the study population, at a mean exposure level of $0.025 \text{ mg Cr(VI)/m}^3$ and a mean time-to-onset of 604 days.

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Ophthalmoscopic examination did not reveal any changes in male and female CDF rats exposed to 30 mg chromium(III)/m³ as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999).

Histopathologic examination of rats exposed to 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years revealed normal morphology of the ocular tissue (Lee et al. 1989).

Body Weight Effects. In a report of a case of acute exposure to "massive amounts" of chromium trioxide fumes, the patient became anorexic and lost 20–25 pounds during a 3-month period following exposure (Meyers 1950).

In rats exposed to an aerosol of sodium dichromate for 30 or 90 days or for 90 days followed by an additional 30 days of nonexposure, body weight gain was significantly decreased at 0.2 and 0.4 mg chromium(VI)/m³ for 30 days ($p < 0.001$), at 0.4 mg chromium(VI)/m³ for 90 days ($p < 0.05$), and at 0.2 ($p < 0.01$) and 0.4 mg chromium(VI)/m³ ($p < 0.05$) in the recovery group (Glaser et al. 1990). There was no effect on body weight gain in rats exposed for 28 days to 0.2 mg/m³ (Glaser et al. 1985) or for ≤ 18 months to 0.1 mg chromium(VI)/m³ as sodium dichromate (Glaser et al. 1986, 1988, 1990) or 0.1 mg chromium(III and VI)/m³ as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988). Body weight was significantly decreased in male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m³ as chromium trioxide mist for 90 days (Kim et al. 2004) and in male, but not female, rats exposed to 10 mg chromium(III)/m³ as chromic oxide for 13 weeks (Derelanko et al. 1999). However, exposure of male and female rats to 30 mg chromium(III)/m³ as basic chromium sulfate for 13 weeks did not produce body weight changes (Derelanko et al. 1999). Similarly, there was no effect on body weight gain in rats exposed to 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years (Lee et al. 1989).

Metabolic Effects. In a study of chromate production workers, a significant increase in plasma total homocysteine levels and decreases in serum vitamin B12 and folate levels were observed; the mean urinary chromium level was 17.41 $\mu\text{g/g}$ creatinine (Wang et al. 2011b). The mean chromium level in air was 27.13 μg chromium/m³ and the mean exposure time was 12.86 years. Erythrocyte chromium levels were significantly correlated with serum vitamin B12 and folate levels, and urinary chromium levels were correlated with vitamin B12 levels. The investigators suggested that the increased homocysteine levels were due to vitamin B12 and folate deficiency and that vitamin B12 and folate deficiency may be secondary to chromium-induced renal damage.

3.2.1.3 Immunological and Lymphoreticular Effects

Sensitization of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies. Although the route of exposure for initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal routes, information on the exposure levels producing sensitization by the inhaled route was not identified. Additional information on contact dermatitis in sensitized workers is provided in Section 3.2.3.3 (Dermal Exposure, Immunological and Lymphoreticular Effects).

Acute reactions have been observed in chromium sensitive individuals exposed to chromium via inhalation as noted in several individual case reports. A 29-year-old welder exposed to chromium vapors from chromium trioxide baths and to chromium and nickel fumes from steel welding for 10 years complained of frequent skin eruptions, dyspnea, and chest tightness. Chromium sensitivity in the individual was measured by a sequence of exposures, via nebulizer, to chromium(VI) as sodium chromate. Exposure to 0.029 mg chromium(VI)/mL as sodium chromate caused an anaphylactoid reaction, characterized by dermatitis, facial angioedema, bronchospasms accompanied by a tripling of plasma histamine levels, and urticaria (Moller et al. 1986). Similar anaphylactoid reactions were observed in five individuals who had a history of contact dermatitis to chromium, after exposure, via nebulizer, to an aerosol containing 0.035 mg chromium(VI)/mL as potassium dichromate. Exposure resulted in decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, nasal blocking, cough, and wheezing (Olaguibel and Basomba 1989). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases produced by the welding process (Keskinen et al. 1980). A 28-year-old construction worker developed work-related symptoms of asthma, which worsened during periods when he was working with (and sawing) corrugated fiber cement containing chromium. A skin patch test to chromium was negative. Asthmatic responses were elicited upon inhalation challenge with fiber cement dust or nebulized potassium chromate (Leroyer et al. 1998). A 40-year-old woman exposed to chromium and nickel in a metalworks company developed occupational asthma and tested positive to skin prick tests and bronchial challenge tests with potassium dichromate (Cruz et al. 2006). In four male workers (two electroplating workers, one welder, and one cement worker) with work-related symptoms of asthma, two tested positive to skin prick tests with potassium dichromate and nickel sulfate and all tested positive to bronchial challenge tests with potassium dichromate and nickel sulfate (Fernandez-Nieto et al. 2006). Chromium-induced asthma may occur in

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some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high.

Concentrations of some lymphocyte subpopulations (CD4⁺ helper-inducer, CD5--CD19⁺ B, CD3--CD25⁺ activated B, and CD3--HLA-DR⁺ activated B and natural killer lymphocytes) were significantly reduced (about 30–50%) in a group of 15 men occupationally exposed to dust containing several compounds (including hexavalent chromium as lead chromate) in a plastics factory. Worker blood lead and urine chromium levels were significantly higher than those of 15 controls not known to be occupationally exposed to toxic agents. Serum chromium concentrations and serum immunoglobulins IgA, IgG, and IgM were not significantly different between the two groups (Boscolo et al. 1997). Mignini et al. (2009) did not find significant differences in lymphocyte subpopulations (CD4⁺, CD8⁺, CD19⁺, CD16⁺/CD56⁺, CD4/CD8) in chromium workers in the shoe, hide, and leather industries, as compared to unexposed workers. The immunological effects of chromium were evaluated in a small group of tannery workers (n=20) in Italy, compared to a matched group of unexposed controls (n=24) (Mignini et al. 2004). Exposure of individual workers was not reported, but monitoring of 20 factories with participating workers reported TWA concentrations of 0.09–0.10 mg total chromium/m³ and 0.001–0.002 mg chromium(VI)/m³. The mean time of employment of the exposed group was 5.8 years. Urine chromium excretion was significantly increased in workers, although no increase in plasma chromium was observed, compared to controls. In workers, proliferative response of peripheral blood mononucleocytes (PBMC) in response to concavalin A was increased approximately 24% compared to controls; no difference between workers and controls were observed for the percent distribution of lymphocyte subsets (e.g., T lymphocytes, T helper lymphocytes, T cytotoxic lymphocytes, B lymphocytes, and natural killer cells). In tannery and chrome-plating workers exposed to high levels of chromium (mean blood chromium level of 86.71 µg/L), no significant alterations in IL-12, as compared to unexposed workers, were found; however, when IL-12 levels were measured in lipopolysaccharide-stimulated peripheral blood monocyte cells, a significant elevation was found in chromium workers (Katiyar et al. 2009). Interferon-γ levels were significantly higher in peripheral blood monocyte cells (with or without stimulation) in chromium workers; a significant correlation between interferon-γ levels (in stimulated cells) and blood chromium levels was also found. In contrast, a study of shoe, hide, and leather industry workers found a significant decrease in IL-12 levels (Mignini et al. 2009). This study also found increases in IL-2 and IL-6 levels, but no changes in IL-1β, tumor necrosis factor-α, interferon-γ, or IL-4 levels. Immune function, as assessed by the lymphocyte proliferative response to mitogens (phytohemagglutinin and concanavalin A) was also significantly altered in this group of workers.

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Immunological effects of exposure to chromic acid were evaluated in 46 electroplating workers in Taiwan (Kuo and Wu 2002). The entire group was employed for an average of 6.1 years. Workers were divided into low (n=19), moderate (n=17), and high (n=10) subgroups based on mean urine chromium excretion of <1.13, 1.14–6.40, and >6.40 μg chromium/g creatinine, respectively. Airborne chromium was measured by personal samplers for all study participants for the duration of one 8-hour shift (data not reported); however, no information was reported on individual or group exposures over the time of employment. A negative correlation was observed between urine chromium and B cell percentage and a positive correlation was observed between urine chromium and blood IL-8 concentration. The study authors report that smoking was an important factor for lymphocyte subsets; thus, interpretation of these results is limited by confounding factors.

An animal study was designed to examine the immunotoxic effects of soluble and insoluble hexavalent chromium agents released during welding (Cohen et al. 1998). Rats exposed to atmospheres containing soluble potassium chromate at 0.36 mg chromium(VI)/ m^3 for 5 hours/day, 5 days/week for 2 or 4 weeks had significantly increased levels of neutrophils and monocytes and decreased alveolar macrophages in bronchoalveolar lavage than air-exposed controls. Significantly increased levels of total recoverable cells were noted at 2 (but not 4) weeks of exposure. In contrast, no alterations in the types of cells recovered from the bronchoalveolar lavage fluid were observed in rats exposed to 0.36 mg chromium(VI)/ m^3 as insoluble barium chromate, as compared to controls. However, the cell types recovered did differ from those recovered from rats exposed to soluble chromium. Changes seen in pulmonary macrophage functionality varied between the soluble and insoluble chromium(VI) exposure groups. The production of interleukin (IL)-1 and tumor necrosis factor (TNF)- α cytokines were reduced in the potassium chromate exposed rats; only TNF- α was decreased in the barium chromate rats. IL-6 levels were not significantly altered in either group. Barium chromate affected zymosan-inducible reactive oxygen intermediate formation and nitric oxide production to a greater degree than soluble chromium(VI). Insoluble chromium(VI) reduced the production of superoxide anion, hydrogen peroxide, and nitric oxide; soluble chromium(VI) only reduced nitric oxide production.

Rats exposed to 0.025–0.2 mg chromium(VI)/ m^3 as sodium dichromate for 28 or 90 days had increased spleen weights at ≥ 0.05 mg chromium(VI)/ m^3 and increased response to sheep red blood cells at ≥ 0.025 mg chromium(VI)/ m^3 . In the 90-day study, serum immunoglobulin content was increased in the 0.05 and 0.1 mg chromium(VI)/ m^3 groups but not in the 0.2 mg chromium(VI)/ m^3 group. There was an increase in mitogen-stimulated T-cell response in the group exposed for 90 days to 0.2 mg

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chromium(VI)/m³. Bronchial alveolar lavage fluid had an increased percentage of lymphocytes in the groups exposed to 0.025 and 0.05 mg chromium(VI)/m³ and an increased percentage of granulocytes in the groups exposed to 0.05 mg chromium(VI)/m³ for 28 days. The phagocytic activity of macrophages was increased in the 0.05 mg chromium(VI)/m³ group. A higher number of macrophages in telophase was observed in the 0.025 and 0.05 mg chromium(VI)/m³ groups. Bronchial alveolar lavage fluid from rats exposed for 90 days had an increased percentage of lymphocytes in the 0.025, 0.05, and 0.2 mg chromium(VI)/m³ groups and an increased percentage of granulocytes and number of macrophages in the 0.05 mg chromium(VI)/m³ groups. The phagocytic activity of the macrophages was increased in the 0.025 mg and 0.05 mg chromium(VI)/m³ groups and decreased in the 0.2 mg chromium(VI)/m³ group. A greater number of macrophages in telophase and an increase in their diameter were observed in the 0.025, 0.05, and 0.2 mg chromium(VI)/m³ groups (Glaser et al. 1985).

Low-level exposure to sodium dichromate seems to stimulate the humoral immune system (as indicated by the significant increase in total immunoglobulin levels); exposure to 0.2 mg chromium(VI)/m³ ceases to stimulate the humoral immune system (significant decreases in total immunoglobulin levels) but still may have effects on the T lymphocytes. The depression in macrophage cell count and phagocytic activities correlated with a 4-fold lower rate of lung clearance for inhaled iron oxide in the 0.2 mg chromium(VI)/m³ group (Glaser et al. 1985).

Intermediate-duration exposure of rats to inhaled chromium(III) compounds produces histopathological alterations to respiratory lymph nodes and tissues. In male and female CDF rats, exposure to 3, 10, and 30 mg chromium(III)/m³ as soluble basic chromium sulfate for 13 weeks resulted in histiocytic cellular infiltration and hyperplasia of peribronchial lymphoid tissue and mediastinal lymph nodes; lymph node enlargement was also observed on necropsy (Derelanko et al. 1999). Following a 13-week recovery period, enlargement, histiocytosis, and hyperplasia of the mediastinal lymph node was observed in rats exposed to 3, 10, and 30 mg chromium(III)/m³ as basic chromium sulfate. Hyperplasia of the mediastinal lymph node was observed in male and female CDF rats exposed to chromium oxide at concentrations of 3, 10, and 30 mg chromium(III)/m³ for 13 weeks (Derelanko et al. 1999). Following a 13-week recovery period, black pigment (trace-to-mild) in peribronchial lymphoid tissue and mediastinal lymph nodes was found in all treatment groups.

The LOAELs for immunological effects in rats are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#) for chromium(VI) and recorded in [Table 3-2](#) and plotted in [Figure 3-2](#) for chromium(III).

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3.2.1.4 Neurological Effects

In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of dizziness, headache, and weakness when they were working over the chromate tanks (Lieberman 1941). Such poor working conditions are unlikely to still occur in the United States because improvements in industrial hygiene have been made over the years. Results of olfactory perceptions tests conducted in workers employed at chromium plating factories in An-San Korea (mean employment duration of 7.9 years) indicate that olfactory recognition thresholds were significantly higher in exposed workers compared to controls (Kitamura et al. 2003). Air concentrations of chromium(VI) ranged from 0.005 to 0.03 mg chromium(VI)/m³ and of chromium(III) ranged from 0.005 to 0.06 mg chromium(III)/m³. Although the cause of this change was not determined, the study authors suggest that chromium may directly affect the olfactory nerve.

No increases in vascular lesions in the central nervous system were evident in a cohort of 3,408 workers from four former facilities that produced chromium compounds from chromite ore in northern New Jersey (Rosenman and Stanbury 1996). The proportionate mortality ratios for white and black men were 78 (61–98) and 68 (44–101), respectively. The subjects were known to have worked in the four facilities sometime between 1937 and 1971 when the last facility closed. Exposure durations ranged from <1 to >20 years.

No information was located regarding neurological effects in humans or animals after inhalation exposure to chromium(III) compounds or in animals after inhalation exposure to chromium(VI) compounds. No histopathological lesions were found in the brain of male Sprague-Dawley rats exposed to 1.15 mg chromium(VI)/m³ as chromium trioxide for 3 months or in male and female CDF rats exposed to 30 mg chromium(III)/m³ as chromic oxide or basic chromium sulfate for 3 months (Derelanko et al. 1999; Kim et al. 2004) or in the brain, spinal cord, or nerve tissues of rats exposed to 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years (Lee et al. 1989). No neurological or behavioral tests were conducted in these studies.

3.2.1.5 Reproductive Effects

Information regarding reproductive effects in humans after inhalation of chromium compounds is limited. Semen quality was evaluated in 61 workers in a chromium sulfate manufacturing plant in India (Kumar et al. 2005). Employment duration and chromium exposure levels were not reported. The study included a control group of 15 unexposed workers. Chromium blood levels in the exposed group were significantly

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increased compared to the control group. Although no effect was observed on semen volume, liquefaction time, or pH or on sperm viability, count, motility, or concentration, a significant increase was observed in the number of morphologically abnormal sperm in exposed workers. In the exposed group, 53% of subjects had less than 30% normal sperm; in the control group, only 10% of subjects had <30% normal sperm. A significant positive correlation ($r=0.301$; $p=0.016$) was observed between blood chromium and the percentage of abnormal sperm in exposed workers. Sperm count and motility were significantly decreased by 47 and 15%, respectively in a group of 21 workers employed at a chrome plating plant in Henan, China, compared to age-matched, unexposed controls (Li et al. 2001). Serum follicle stimulating hormone (FSH) concentration was significantly increased by 204% and semen lactate dehydrogenase activity was significantly decreased by 30% in exposed compared to control workers, although no effect on serum luteinizing hormone (LH) concentration was observed. Serum chromium levels were 11% higher in the exposed workers compared to control; however, the increase was not statistically significant. Duration of employment for all study participants ranged from 1 to 15 years; no information on exposure levels or demographics of the exposed and control groups were reported.

The effect of chromium(VI) on the course of pregnancy and childbirth was studied in women employees at a dichromate manufacturing facility in Russia. Complications during pregnancy and childbirth (not further described) were reported in 20 of 26 exposed women who had high levels of chromium in blood and urine, compared with 6 of 20 women in the control group. Toxicosis (not further described) was reported in 12 exposed women and 4 controls. Postnatal hemorrhage occurred in four exposed and two control women (Shmitova 1980). Similar results were reported in a more extensive study of 407 women who worked at a factory producing chromium compounds (not otherwise specified) compared with 323 controls. The frequency of birth complications was 71.4% in a subgroup of highly exposed women, 77.4% in a subgroup of women with a lower level of exposure, and 44.2% in controls. Toxicosis in the first half of pregnancy occurred in 35.1% of the high exposure group, 33.3% of the low exposure group, and 13.6% of the controls. The frequency of postnatal hemorrhage was 19.0% for the high exposure group and 5.2% in controls (Shmitova 1978). Because these studies were generally of poor quality and the results were poorly reported, no conclusions can be made regarding the potential for chromium to produce reproductive effects in humans.

The occurrence of spontaneous abortion among 2,520 pregnancies of spouses of 1,715 married Danish metal workers exposed to hexavalent chromium from 1977 through 1987 were examined (Hjollund et al. 1995). Occupational histories were collected from questionnaires and information on spontaneous abortion, live births, and induced abortion was obtained from national medical registers. The number of

spontaneous abortions was not increased for pregnant women whose spouses worked in the stainless steel welding industry when compared to controls (odds ratio 0.78, 95% confidence interval [CI] 0.55–1.1). The authors believed that the risk estimate was robust enough that factors such as maternal age and parity and smoking and alcohol consumptions were not confounders. There was no association found in spontaneous abortions in women whose husbands were in the cohort subpopulations who were mild steel welders and metal-arc stainless steel welders, which would lead to higher exposures to welding fumes (workplace chromium exposures not provided). This more recent study does not corroborate earlier findings (Bonde et al. 1992) that showed that wives of stainless steel welders were at higher risk of spontaneous abortions. The current study was based on abortions recorded in a hospital register, while the earlier study was based on self-reporting data. The latter study probably included more early abortions and was biased because the job exposure of male metal workers is apparently modified by the outcome of their partners' first pregnancy.

Histopathological examination of the testes of rats exposed to 0.2 mg chromium(VI)/m³ as sodium dichromate for 28 or 90 days (Glaser et al. 1985), to 0.1 mg chromium(VI)/m³ as sodium dichromate for 18 months, or to 0.1 mg chromium/m³ as a 3:2 mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months (Glaser et al. 1986, 1988) revealed no abnormalities. For intermediate-duration exposures to chromium(III) compounds, no histopathological changes to the reproductive tissues in male and female CDF rats exposed to 30 mg chromium(III)/m³ as chromic oxide or basic chromium sulfate for 3 months; treatment also had no effect on sperm count, motility, or morphology (Derelanko et al. 1999). No histopathological lesions were observed in the prostate, seminal vesicle, testes, or epididymis of male rats or in the uterus, mammary gland, or ovaries of female rats exposed to 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years (Lee et al. 1989).

The NOAELs for reproductive effects in rats are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#) for chromium(VI) and recorded in [Table 3-2](#) and plotted in [Figure 3-2](#) for chromium(III).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to chromium or its compounds.

3.2.1.7 Cancer

Occupational exposure to chromium(VI) compounds in various industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, ferrochromium alloy production, and leather tanning. Compilations and discussion of many of these studies can be found in reviews of the subject (Goldbohm et al. 2006; IARC 1990; Steenland et al. 1996). Studies of chromium workers have varied considerably in strength of design for determining cancer risks related to chromium exposure. The strongest designs have provided estimates of chromium(VI) (or exposure to other chromium species) for individual members of the cohorts, enabling application of dose-response analysis to estimate the contribution of chromium exposure to cancer risk. Studies that do not provide estimates of chromium exposure have relied on surrogate dose metrics (e.g., length of employment at job titles associated with chromium exposure) for exploring attribution of cancer risk to chromium exposure. However, these surrogate measures are often strongly correlated with exposures to other work place hazards, making conclusions regarding possible associations with chromium exposures more uncertain. Chromium dose-response relationships have been reported for chromate production workers, but not for other categories of chromium workers. In studies of chromate production workers, increased risk of respiratory tract cancers have been found in association with increased cumulative exposure to chromium(VI) and several estimates of excess lifetime risk attributed to chromium exposure have been reported. Studies of chrome platers, who were exposed to chromium(VI) and other carcinogenic chemicals, including nickel, have found significant elevations in lung cancer risk in association with surrogate indicators of chromium exposure, such as duration of employment at jobs in which exposure to chromium occurred; however, estimates of risk attributable specifically to chromium exposure have not been reported. Results of studies in stainless steel welders exposed to chromium(VI) and other chemicals, and in ferrochromium alloy workers, who were exposed mainly to chromium(0) and chromium(III), but also to some chromium(VI), have been mixed and are inconclusive with respect to work-associated elevations in cancer rates. Studies in leather tanners, who are exposed to chromium(III), have not found elevated cancer rates. A summary of select occupational exposure studies that were considered the best conducted for each type of chromium work is presented in [Table 3-3](#).

Chromate Production. Numerous studies of cancer mortality among chromate production workers have been reported (Alderson et al. 1981; Bidstrup and Case 1956; Buckell and Harvey 1951; Crump et al. 2003; Davies et al. 1991; Enterline 1974; Gibb et al. 2000b; Korallus et al. 1982; Mancuso 1997a; Ohsaki

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Table 3-3. Risk of Cancer Mortality in Chromium Workers

Cancer type	Risk (95% CI)	Comments	Reference
Chromate production			
Lung cancer	RR 1.80 (1.49–2.14)	2,357 males. Cancer rate ratio of 2.44 (1.54–3.83) associated with a cumulative 45-year exposure to 1 mg/m ³ -year (Park et al. 2004)	Gibb et al. 2000b
Lung cancer	SMR 268 (200–352)	U.S. reference rate; SMR of 241 (180–317) using Ohio reference males; lung cancer mortality risk increased with cumulative chromium exposure levels, duration of exposure, and year of hire; a high percentage (73–86%) of workers smoked	Luippold et al. 2003
Chromate pigment workers			
Lung cancer	SMR 190 (111–295)	Workers employed >30 years; no significant alterations in workers with shorter employment; chromium levels monitored in later years were >0.5 and >2 mg/m ³ for highly exposed jobs	Hayes et al. 1989
Chrome plating			
Lung cancer	SMR 172 (112–277)	Males and females in chrome bath area for >1 year; SMR for workers in chrome bath area for >5 years was 320 (128–658); significant positive trend for lung cancer mortality and duration of exposure found in male chrome bath workers	Sorahan et al. 1998
Lung cancer	SMR 1.59 (1.01–2.38)	Workers with initial chromium exposure prior to 1970	Hara et al. 2010
Malignant lymphoma	SMR 3.80 (1.39–8.20)	Workers with initial chromium exposure prior to 1970	Hara et al. 2010
Stainless steel production and welding			
Lung cancer	SMR 2.49 (0.80–5.81)	Not significant when compared to national rates; significant increase when compared with an internal reference group and stratified for age; average chromium(VI) concentration in 1975 was 0.11 mg/m ³	Sjogren et al. 1987
Lung cancer	SMR 2.29 (1.14–4.09)	SMR for stainless steel foundry workers; SMR for workers employed >30 years was 3.24 (95% CI=1.19–7.05); no increase in lung cancer deaths in workers involved in melting and casting stainless steel	Moulin et al. 1993

CI = confidence interval; RR = relative risk; SMR = standardized mortality ratio

et al. 1978; Park and Stayner 2006; Park et al. 2004; Pastides et al. 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1994; Taylor 1966). Collectively, these studies provide evidence for associations between lung cancer mortality and employment in chromate production, with risks declining with improved industrial hygiene. Less consistently, nasal cancers have been observed (Alderson et al. 1981; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1994). Evidence for associations between exposure to chromium and cancer is strongest for lung cancer mortality, which has been corroborated and quantified in numerous studies. A meta-analysis of 49 epidemiology studies based on 84 papers of cancer outcomes, primarily among chromium workers, found SMRs ranging from 112 to 279 for lung cancer, with and overall SMR of 141 (95% CI 135–147; Cole and Rodu 2005). When limited to high-quality studies controlled for smoking, the overall SMR for lung cancer was 112 (95% CI 104–119). SMRs for other forms of cancer from studies that controlled for confounders were not elevated. Several studies have attempted to derive dose-response relationships for this association (Crump et al. 2003; Gibb et al. 2000b; Mancuso 1997a; Park and Stayner 2006; Park et al. 2004). These studies are particularly important because they have included individual exposure estimates to chromium for each member of the cohort based on work place monitoring; dose-response modeling to ascertain the contribution of changing exposures to chromium to risk (in workers who were also exposed to other work-place hazards that could have contributed to cancer risk); and evaluation of the impacts of potential co-variables and confounders (e.g., age, birth cohort, and smoking) on chromium-associated risk.

Gibb et al. (2000b) examined lung cancer mortality in a cohort of chromate production workers (n=2,357, males) in Baltimore, Maryland, who were first hired during the period 1950–1974, with mortality followed through 1992. This cohort was the subject of numerous earlier studies, which found significantly increased lung cancer mortality (i.e., standard mortality ratios) among workers at the plant (Baetjer 1950; Braver et al. 1985; Hayes et al. 1979; Hill and Ferguson 1979). In the Gibb et al. (2000b) study, cumulative exposures to chromium(VI) or chromium(III) (mg/m³-year) were reconstructed for each member of the cohort from historical workplace air monitoring data and job title records (Gibb et al. 2000b). Lung cancer for the entire group had a relative risk of 1.80 (95% CI 1.49–2.14). Relative risk of lung cancer mortality (adjusted for smoking) increased by a factor to 1.38 (95% CI 1.20–1.63) in association with a 10-fold increase in cumulative exposure to chromium(VI). The analogous relative risk for cumulative exposure to chromium(III) was 1.32 (95% CI 1.15–1.51). Exposures to chromium(III) and chromium(VI) were highly correlated; therefore, discrimination of risks associated with either were problematic. However, in a combined model that included cumulative exposure to both chromium species, relative risk for chromium(VI) exposure remained significant (1.66, p=0.045), whereas relative risk for chromium(III) was negative (-0.17, p=0.4). This outcome suggests that exposure to

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chromium(VI), rather than chromium(III), was the dominant (if not sole) contributor to lung cancer risk (after adjustments for smoking). Park et al. (2004) reanalyzed the data for the Baltimore, Maryland cohort using a variety of dose-response models. In the preferred model (linear with cumulative chromium exposure and log-linear for age, smoking, race), cancer rate ratio for a 45-year cumulative exposure to 1 mg/m^3 -year of chromium(VI) was estimated to be 2.44 (95% CI 1.54–3.83). This corresponded to an excess lifetime risk unit risk (i.e., additional lifetime risk from occupational exposure to $1 \text{ } \mu\text{g CrO}_3/\text{m}^3$ or $0.52 \text{ } \mu\text{g Cr(VI)}/\text{m}^3$) of 0.003 (95% CI 0.001–0.006) or to $100 \text{ } \mu\text{g chromium(VI)}/\text{m}^3$ of 0.255 (95% CI 0.109–0.416). Subsequent analyses conducted by Park and Stayner (2006) attempted to estimate possible thresholds for increasing lung cancer risk. This analysis was able to exclude possible thresholds in excess of $16 \text{ } \mu\text{g/m}^3$ chromium(VI) or 0.4 mg/m^3 -year cumulative exposure to chromium(VI).

Several studies have examined cancer mortality in a cohort of chromate production workers in Painesville, Ohio, and have found increased lung cancer mortality (e.g., SMRs) among workers at the plant (Crump et al. 2003; Luippold et al. 2003; Mancuso 1997a; Mancuso and Hueper 1951). Mancuso (1997a) reconstructed cumulative exposure histories of individual members of the cohort ($n=332$), hired during the period 1931–1937 and followed through 1993. The exposure estimations were based on historical workplace air monitoring data for soluble and insoluble chromium and job title records. Age-adjusted death rates from lung cancer were estimated for cumulative exposure strata, and increased with increasing cumulative exposure to total chromium, insoluble chromium, and soluble chromium (a dose response model was not reported). The highest rates were observed in soluble chromium strata $>4 \text{ mg/m}^3$ -years (2,848 per 100,000). Death rates were not adjusted for smoking, which would have been a major contributor to lung cancer death rates in the cohort. Although the study discriminated exposures to soluble and insoluble chromium, these classifications are not adequate surrogates for exposures to trivalent or hexavalent chromium (Kimbrough et al. 1999; Mundt and Dell 1997); therefore, the study cannot attribute risk specifically to either species. More recent studies of this cohort have attempted to reconstruct individual exposure histories to chromium(VI), based on species-specific air monitoring data, and have attempted to quantify the potential contribution of smoking to lung cancer risk (Crump et al. 2003; Luippold et al. 2003). These studies included workers ($n=482$) hired after 1940 and followed through 1997. Increasing lung cancer risk was significantly associated with increasing cumulative exposure to chromium(VI). Relative risk for lung cancer mortality was estimated to be 0.794 per mg/m^3 -year (90% CI 0.518–1.120). The analogous additive risk was 0.00161 per mg/m^3 -year per person year (90% CI 0.00107–0.00225). These estimates correspond to unit risks (i.e., additional lifetime risk from occupational exposure to $1 \text{ } \mu\text{g/m}^3$) of 0.00205 (90% CI 0.00134–0.00291), based on the relative risk Poison model, and 0.00216 (90% CI 0.00143–0.00302), based on the additional risk Poison model. Risk

estimates were not appreciably sensitive to birth cohort or to smoking designation (for the 41% of the cohort that could be classified). The latter outcome suggests that smoking did not have a substantial effect on chromium(VI) associated lung cancer risk (i.e., smoking and chromium appeared to contribute independently to cancer risk).

A meta-analysis of the Crump et al. (2003); Gibb et al. (2000b), and Mancuso (1997a) studies has also been reported (Goldbohm et al. 2006). Excess lifetime risk of lung cancers was estimated from a life table analysis (using Dutch population vital statistics) and estimates of relative risk from each study, or in the case of Mancuso (1997a), estimated in the meta-analysis (approximately 0.0015 per $\text{mg}/\text{m}^3\text{-year}$). Estimates of excess lifetime risks (deaths attributed to a 40-year occupational exposure to chromium(VI) at $1 \mu\text{g}/\text{m}^3$, for survival up to age 80 years) were 0.0025, 0.0048, and 0.0133, based on Crump et al. (2003), Mancuso et al. (1997a), and Gibb et al. (2000b), respectively.

In conclusion, despite limitations of some studies, occupational exposure to chromium(VI) in the chromate production industry is associated with increased risk of respiratory cancer. Estimates of excess lifetime occupational risks range from 0.002 to 0.005 per $\mu\text{g}/\text{m}^3$ of chromium(VI). Changes in production process and industrial hygiene appear to have reduced overall risk over the past 30–40 years.

Chromate Pigments Production and Use. Studies of workers engaged in the production of chromate pigments provide evidence for increased risk of lung cancer associated with employment in work areas where exposure to chromium compounds occurred. However, the contribution of chromium exposure to cancer risk in these cohorts remains uncertain for several reasons: (1) members of the cohorts experienced exposures to a variety of chemicals that may have contributed to cancer (e.g., nickel); (2) exposures of the individual cohort members to chromium were not quantified or subjected to exposure-response analysis; and (3) dose metrics used in dose-response analysis were measures of employment duration, which are highly correlated with exposures to chemical hazards other than chromium. Nevertheless, these studies have found elevated lung cancer rates in chromium pigment workers in comparison to reference populations (e.g., SMRs) and, in some studies, increased lung cancer rates in association with increased potential (e.g., job type, employment duration) for exposure to chromium (Dalager et al. 1980; Davies 1979, 1984; Franchini et al. 1983; Frentzel-Beyme 1983; Haguenoer et al. 1981; Hayes et al. 1989; Langård and Norseth 1975; Langård and Vigander 1983; Sheffet et al. 1982).

Chrome Plating. Studies of chrome platers provide evidence for increased risk of lung cancer associated with employment in work areas where exposure to chromium compounds occurred. However, the contribution of chromium exposure to cancer risk in these cohorts remains uncertain for several reasons: members of the cohorts experienced exposures to a variety of chemicals that may have contributed to (1) cancer (e.g., nickel, sulfuric acid); (2) exposures of the individual cohort members to chromium were not quantified or subjected to exposure-response analysis; and (3) dose metrics used in dose-response analysis were measures of employment duration, which are highly correlated with exposures to chemical hazards other than chromium. Nevertheless, these studies have found elevated lung cancer rates in chrome bath workers in comparison to reference populations (e.g., standard mortality ratios) who were exposed primarily to soluble chromium(VI) (e.g., chromic acid mists) and, in some studies, increased lung cancer rates in association with increased potential (e.g., job type, employment duration) for exposure to chromium (Dalager et al. 1980; Guillemin and Berode 1978; Hanslian et al. 1967; Okubo and Tsuchiya 1977, 1979; Royle 1975a; Silverstein et al. 1981; Sorahan et al. 1987, 1998; Takahashi and Okubo 1990).

Sorahan et al. (1998) examined lung cancer risks in a cohort of nickel/chrome platters (n=1,762, hired during the period 1946–1975 with mortality follow-up through 1995). The same cohort was studied by Royle (1975a). Significant excess risks of lung cancer were observed among males and females working in the chrome bath area for <1 year (SMR=172; 95% CI 112–277; p<0.05) or >5 years (SMR=320; 95% CI 128–658; p<0.001), females working in the chrome bath area for <1 year (SMR=245; 95% CI 118–451; p<0.5), males starting chrome work in the period of 1951–1955 (SMR=210; 95% CI 132–317; p<0.01), and in male chrome workers 10–19 years after first chrome work (SMR=203; 95% CI 121–321; p<0.01). A significant (p<0.01) positive trend for lung cancer mortality and duration of exposure was found for the male chrome bath workers, but not for the female workers. Lung cancer mortality risks were also examined using an internal standard approach, in which mortality in chrome workers was compared to mortality in workers without chromium exposure. After adjusting for sex, age, calendar period, year of starting chrome work, period from first chrome work, and employment status, a significant positive trend (p<0.05) between duration of chrome bath work and lung cancer mortality risk was found.

Hara et al. (2010) conducted a follow-up of the cohort studied by Takahashi and Okubo (1990). The study comprised 1,193 male workers of which 626 had ≥6 months of experience in chromium plating and 567 had no lifetime chromium exposure but ≥6 months plating experience using metals other than chromium. The expected number of deaths was determined by multiplying the number of person-years of observation by cause-, gender-, and age-specific national death rates for each year from 1976–2003. The

analyses found a nonsignificant elevation of lung cancer mortality among a chromium plater subgroup (SMR=1.46; 95% CI 0.98–2.04) (Hara et al. 2010). However, the study found significant elevations for mortality due to brain tumors (SMR=9.14; 95% CI 1.81–22.09) and malignant lymphoma (SMR=2.84; 95% CI 1.05–5.51). It should be noted, however, that the risk for brain tumors was based on only three observed cases versus 0.3 expected. Analyses according to the follow-up period, exposure duration, and year of first exposure showed that risks were elevated for lung cancer (SMR=1.59, 95% CI 1.01–2.38) and malignant lymphoma (SMR=3.80; 95% CI 1.39–8.29) among those with initial chromium exposure prior to 1970.

Stainless Steel Production and Welding. Workers in the stainless steel welding industry are exposed to chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer (e.g., nickel); however, results of studies of cancer mortality in these populations have been mixed. Some studies have found increased cancer mortality rates among workers; however, examinations of possible associations with exposures to chromium have not been reported. A study of 1,221 stainless steel welders in the former Federal Republic of Germany found no increased risk of lung cancer or any other specific type of malignancy compared with 1,694 workers involved with mechanical processing (not exposed to airborne welding fumes) or with the general population of the former Federal Republic of Germany (Becker et al. 1985). A follow-up study (Becker 1999) which extended the observation period to 1995, found similar results for lung (includes bronchus and trachea) cancer (SMR=121.5, 95% CI 80.7–175.6). An excess risk of pleura mesothelioma was observed (SMR=1,179.9; 95% CI=473.1–2430.5); however, this was attributed to asbestos exposure. A study of 234 workers from eight companies in Sweden, who had welded stainless steel for at least 5 years during the period of 1950–1965 and followed until 1984, found five deaths from pulmonary tumors, compared with two expected (SMR=2.49; 95% CI=0.80–5.81), based on the national rates for Sweden. The excess was not statistically significant. However, when the incidence of lung cancer in the stainless steel welders was compared with an internal reference group, a significant difference was found after stratification for age. The average concentration of chromium(VI) in workroom air from stainless steel welding, determined in 1975, was reported as 0.11 mg/m³ (Sjogren et al. 1987). The cohort in this study was small, and stainless welders were also exposed to nickel fumes. Smoking was probably not a confounding factor in the comparisons with the internal reference group.

In a study of the mortality patterns in a cohort of 4,227 workers involved in the production of stainless steel from 1968 to 1984, information was collected from individual job histories, and smoking habits were obtained from interviews with workers still active during the data collection (Moulin et al. 1993). The observed number of deaths was compared to expected deaths based on national rates and matched for

age, sex, and calendar time. No significant excess risk of lung cancer was noted among workers employed in melting and casting stainless steel (SMR=1.04; 95% CI=0.42–2.15). However, there was a significant excess among stainless steel foundry workers (SMR=2.29; 95% CI=1.14–4.09). The SMR increased for workers with length of employment over 30 years to 3.24 (95% CI=1.19–7.05). No measurements of exposure were provided.

Ferrochromium Production. Workers in the ferrochromium alloy industry are exposed to chromium(III) and chromium(VI) compounds, as well as other chemical hazards that could contribute to cancer; however, results of studies of cancer mortality in these populations have been mixed. No significant increase in the incidence of lung cancer was found among 1,876 employees who worked in a ferrochromium plant in Sweden for at least 1 year from 1930 to 1975 compared with the expected rates for the county in which the factory was located. The workers had been exposed mainly to metallic chromium and chromium(III), but chromium(VI) was also present. The estimated levels ranged from 0 to 2.5 mg chromium(0) and chromium(III)/m³ and from 0 to 0.25 mg chromium(VI)/m³ (Axelsson et al. 1980). An excess of lung cancer was found in a study of 325 male workers employed for >1 year in a ferrochromium producing factory in Norway between 1928 and 1977 (Langård et al. 1980), and whose employment began before 1960 (SMR=850, p=0.026); however, in a follow-up of this cohort (n=379, hired before 1965 and followed through 1985), the SMR for lung cancer was not significant (SMR=154; Langård et al. 1990). Workroom monitoring in 1975 indicated that the ferrochromium furnace operators worked in an atmosphere with 0.04–0.29 mg total chromium/m³, with 11–33% of the total chromium as chromium(VI) (Langård et al. 1980).

An ecological study examined the distribution of lung cancer cases in Dolný Kubín in the Slovak Republic where ferrochromium production facility was located. Cases were stratified into three groups (males): ferrochromium workers (n=59), workers (n=106) thought not to have been exposed to chromium, and residents (n=409) who were not thought to have had appreciable exposure to chromium. Lung cancer rates were higher in the chromium workers (320 per 1,000 per year, 95% CI 318–323) compared to workers (112, 95% CI 109–113) and residents (79, 95% CI 76–80) who were not thought to have been exposed to chromium (relative risk=4.04 for chromium workers compared to residents). Mean work shift air concentrations in the smelter were 0.03–0.19 mg/m³ for total chromium and 0.018–0.03 mg/m³ for chromium(VI). These estimates were not adjusted for smoking or other potential co-variables that might have contributed to cancer rates in the chromium workers.

Leather Tanning. Studies of workers in tanneries, where exposure is mainly to chromium(III), in the United States (0.002–0.054 mg total chromium/m³) (Stern et al. 1987), the United Kingdom (no concentration specified) (Pippard et al. 1985), and the Federal Republic of Germany (no concentration specified) (Korallus et al. 1974a) reported no association between exposure to chromium(III) and excess risk of cancer.

Mixed Occupations. Beveridge et al. (2010) examined the link between exposure to chromium(VI) exposure and lung cancer among workers in occupations that generally entail lower levels of exposure than those seen in historical cohorts; the most prevalent occupations were construction painters, sheet metal workers, and mechanics. Analysis of the pooled data did not show a significant association between lung cancer and exposure to chromium(VI) (OR=1.1, 95% CI 0.9–1.5). Subdividing the exposed subjects into those with substantial exposure to chromium(VI) and those with nonsubstantial exposure showed both groups having similar nonsignificantly increased risks. However, a significantly increased risk for lung cancer was found among exposed nonsmokers (OR=1.2, 95% CI 1.2–4.8), but not among smokers (OR=1.0, 95% CI 0.7–1.3). The investigators suggested that the greater ability to detect risk in nonsmokers could be the result of a cleaner, although imprecise, indication of chromium's actual effects.

The relationship between occupational exposure to chromium(VI) and cancers other than lung cancer has also been explored. Gatto et al. (2010) conducted meta-analyses of 32 studies of gastrointestinal tract cancers that met specific inclusion criteria. Inclusion criteria included: (1) epidemiologic studies published after 1950 of populations with occupational exposure to chromium(VI) through either inhalation or ingestion routes; (2) exposure or potential exposure to chromium(VI) was stated explicitly, or the cohort was from an industry recognized as having exposure to chromium(VI); (3) morbidity or mortality from one of the following cancers was studied: oral cavity, esophageal, stomach, small intestine, colon, or rectum; and (4) measures of effect were estimated in the study, or data were available that allowed for the calculation of a relative risk estimate and 95% CI. Meta-analysis summary relative risk measures were calculated using random effects models and inverse variance weighting methods. The following meta-SMRs (95% CI) were obtained: oral cavity 1.02 (0.77–1.34), esophagus 1.17 (0.90–1.51), stomach 1.09 (0.93–1.28), colon 0.89 (0.70–1.12), and rectum 1.17 (0.98–1.39). Analyses of subgroups subjected to higher exposure resulted in an elevated meta-SMR of 1.49 (95% CI 1.06–2.09) only for esophageal cancer among U.S. cohorts. However, this finding was based on a subgroup of only four studies, one of which was a proportionate mortality ratio study. Only three studies reported relative risks estimated for small intestine cancer and in none of them was there a statistically significant increased risk. The main limitation of the meta-analyses, acknowledged by the investigators, was the inability to control

for potential confounding by smoking and other confounders such as excessive alcohol consumption, dietary factors, and socioeconomic status. The overall conclusion was that workers exposed to chromium(VI) are not at a greater risk of gastrointestinal cancers than the general population.

Environmental Exposure. In addition to the occupational studies, a retrospective environmental epidemiology study was conducted of 810 lung cancer deaths in residents of a county in Sweden where two ferrochromium alloy industries are located. No indication was found that residence near these industries is associated with an increased risk of lung cancer (Axelsson and Rylander 1980).

A retrospective mortality study conducted on a population that resided in a polluted area near an alloy plant that smelted chromium in the People's Republic of China found increased incidences of lung and stomach cancer. The alloy plant began smelting chromium in 1961 and began regular production in 1965, at which time sewage containing chromium(VI) dramatically increased. The population was followed from 1970 to 1978. The size of the population was not reported. The adjusted mortality rates of the exposed population ranged from 71.89 to 92.66 per 100,000, compared with 65.4 per 100,000 in the general population of the district. The adjusted mortality rates for lung cancer ranged from 13.17 to 21.39 per 100,000 compared with 11.21 per 100,000 in the general population. The adjusted mortality rates for stomach cancer ranged from 27.67 to 55.17 per 100,000 and were reported to be higher than the average rate for the whole district (control rates not reported). The higher cancer rates were found for those who lived closer to the dump site (Zhang and Li 1987). Attempts to abate the pollution from chromium(VI) introduced in 1967 also resulted in additional pollution from sulfate and chloride compounds. It was not possible to estimate exposure levels based on the description of the pollution process. Exposure of this population was mainly due to chromium(VI) in drinking water, although air exposure cannot be ruled out.

The studies in workers exposed to chromium compounds clearly indicate that occupational exposure to chromium(VI) is associated with an increased risk of respiratory cancer. Using data from the Mancuso (1975) study and a dose-response model that is linear at low doses, EPA derived a unit risk estimate of 1.2×10^{-2} for exposure to air containing $1 \mu\text{g chromium(VI)/m}^3$ (or potency of $1.2 \times 10^{-2} [\mu\text{g/m}^3]^{-1}$) (IRIS 2011).

Chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice exposed to $4.3 \text{ mg chromium(VI)/m}^3$ as calcium chromate had a 2.8-fold greater incidence of lung tumors,

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compared to controls (Nettesheim et al. 1971). Lung tumors were observed in 3/19 rats exposed to 0.1 mg chromium(VI)/m³ as sodium dichromate for 18 months, followed by 12 months of observation. The tumors included two adenomas and one adenocarcinoma. No lung tumors were observed in 37 controls or the rats exposed to ≤ 0.05 mg chromium(VI)/m³ (Glaser et al. 1986, 1988). The increased incidence of lung tumors in the treated rats was significant by the Fisher Exact Test ($p=0.03$) performed by Syracuse Research Corporation.

Several chronic animal studies reported no carcinogenic effects in rats, rabbits, or guinea pigs exposed to ≈ 1.6 mg chromium(VI)/m³ as potassium dichromate or chromium dust 4 hours/day, 5 days/week (Baetjer et al. 1959b; Steffee and Baetjer 1965).

Rats exposed to ≤ 15.5 mg chromium(IV)/m³ as chromium dioxide for 2 years had no statistically significant increased incidence of tumors (Lee et al. 1989).

The Cancer Effect Levels (CELs) are recorded in [Table 3-1](#) and plotted in [Figure 3-1](#).

3.2.2 Oral Exposure

3.2.2.1 Death

Cases of accidental or intentional ingestion of chromium that have resulted in death have been reported in the past and continue to be reported even in more recent literature. In many cases, the amount of ingested chromium was unknown, but the case reports provide information on the sequelae leading to death. For example, a 22-month-old boy died 18.5 hours after ingesting an unknown amount of a sodium dichromate solution despite gastric lavage, continual attempts to resuscitate him from cardiopulmonary arrest, and other treatments at a hospital. Autopsy revealed generalized edema, pulmonary edema, severe bronchitis, acute bronchopneumonia, early hypoxic changes in the myocardium, liver congestion, and necrosis of the liver, renal tubules, and gastrointestinal tract (Ellis et al. 1982). Another case report of a 1-year-old girl who died after ingesting an unknown amount of ammonium dichromate reported severe dehydration, caustic burns in the mouth and pharynx, blood in the vomitus, diarrhea, irregular respiration, and labored breathing. The ultimate cause of death was shock and hemorrhage into the small intestine (Reichelderfer 1968).

Several reports were available in which the amount of ingested chromium(VI) compound could be estimated. A 17-year-old male died after ingesting 29 mg chromium(VI)/kg as potassium dichromate in a

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suicide. Despite attempts to save his life, he died 14 hours after ingestion from respiratory distress with severe hemorrhages. Caustic burns in the stomach and duodenum and gastrointestinal hemorrhage were also found (Clochesy 1984; Iserson et al. 1983). A 35-year-old female died after ingesting approximately 25 g chromium(VI) (357 mg chromium(VI)/kg assuming 70 kg body weight) as chromic acid in a suicide (Loubieres et al. 1999). The patient died of multiple organ failure. Terminal laboratory analysis and autopsy revealed metabolic acidosis, gastrointestinal hemorrhage and necrosis, fatty degeneration of the liver, and acute renal failure and necrosis.

A few reports have described death of humans after ingesting lower doses of chromium(VI). In one case, a 14-year-old boy died 8 days after admission to the hospital following ingestion of 7.5 mg chromium(VI)/kg as potassium dichromate from his chemistry set. Death was preceded by gastrointestinal ulceration and severe liver and kidney damage (Kaufman et al. 1970). In another case, a 44-year-old man died of severe gastrointestinal hemorrhage 1 month after ingesting 4.1 mg chromium(VI)/kg as chromic acid (Saryan and Reedy 1988).

Acute oral LD₅₀ values in rats exposed to chromium(III) or chromium(VI) compounds varied with the compound and the sex of the rat. LD₅₀ values for chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) range from 13 to 19 mg chromium(VI)/kg in female rats and from 21 to 28 mg chromium(VI)/kg in male rats (Gad et al. 1986). LD₅₀ values of 108 (female rats) and 249 (male rats) mg chromium(VI)/kg for calcium chromate were reported by Vernot et al. (1977). The LD₅₀ values for chromium trioxide were 25 and 29 mg chromium(VI)/kg for female and male rats, respectively (American Chrome and Chemicals 1989). An LD₅₀ of 811 mg chromium(VI)/kg as strontium chromate was reported for male rats (Shubochkin and Pokhodzie 1980). Twenty percent mortality was observed when female Swiss Albino mice were exposed to potassium dichromate(VI) in drinking water at a dose of 169 mg chromium(VI)/kg/day (Junaid et al. 1996a). Similar exposure to a dose level of 89 mg chromium(VI)/kg/day resulted in 15% mortality among female rats of the Druckrey strain (Kanojia et al. 1998). The disparity between this dose and the LD₅₀ identified in the Gad et al. (1986) study may be due to the route of administration, drinking water versus gavage. Chromium(III) compounds are less toxic than chromium(VI) compounds, with LD₅₀ values in rats of 2,365 mg chromium(III)/kg as chromium acetate (Smyth et al. 1969) and 183 and 200 mg chromium(III)/kg as chromium nitrate in female and male rats, respectively (Vernot et al. 1977). The lower toxicity of chromium(III) acetate compared with chromium(III) nitrate may be related to solubility; chromium(III) acetate is less soluble in water than is chromium(III) nitrate. Signs of toxicity included hypoactivity, lacrimation, mydriasis, diarrhea, and change in body weight. Treatment with the

chromium(III) dietary supplement chromium nicotinate of male and female rats resulted in no mortality at doses up to >621.6 mg/kg/day (Shara et al. 2005). The LD₅₀ values for chromium(VI) or chromium(III) compounds indicate that female rats are slightly more sensitive to the toxic effects of chromium(VI) or chromium(III) than male rats. LD₅₀ values in rats are recorded in [Table 3-4](#) and plotted in [Figure 3-3](#) for chromium(VI) and recorded in [Table 3-5](#) and plotted in [Figure 3-4](#) for chromium(III).

Intermediate and chronic exposure of rats and mice to chromium(III) or chromium(VI) compounds did not decrease survival. Survival was not affected in rats and mice exposed to chromium(VI) as sodium dichromate dihydrate in drinking water at doses up to 20.9 and 27.9 mg chromium(VI)/kg/day, respectively, for 3 months (NTP 2007) or at doses up to 7.0 and 8.7 mg chromium(VI)/kg/day, respectively, for 2 years (NTP 2008a). Mortality was not increased in rats fed 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975) or in rats and mice fed up to 313 and 781 mg chromium(III)/kg/day, respectively, as chromium picolinate in the diet for 2 years (NTP 2008b).

3.2.2.2 Systemic Effects

The systemic effects of oral exposure to chromium(III) and chromium(VI) compounds are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in [Table 3-4](#) and plotted in [Figure 3-3](#) for chromium(VI) and recorded in [Table 3-5](#) and plotted in [Figure 3-4](#) for chromium(III).

Respiratory Effects. Case reports of humans who died after ingesting chromium(VI) compounds have described respiratory effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed pleural effusion, pulmonary edema, severe bronchitis, and acute bronchopneumonia (Ellis et al. 1982). Autopsy of a 17-year-old male who committed suicide by ingesting 29 mg chromium(VI)/kg as potassium dichromate revealed congested lungs with blood-tinged bilateral pleural effusions (Clochesy 1984; Iserson et al. 1983). Respiratory effects were not reported at nonlethal doses. No information was identified on respiratory effects in humans after oral exposure to chromium(III) compounds.

No studies were identified regarding respiratory function in animals after oral exposure to chromium(VI) or chromium(III) compounds. The histopathology of lung and nasal tissue has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference	Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)			
ACUTE EXPOSURE								
Death								
1	Human	once (IN)			29 M (death)	Clochesy 1984; Iserson et al. 1983	K2Cr2O7 (VI)	17-year-old, 60 kg boy ingested 5 g potassium dichromate [1,750 mg Cr(VI)]; dose = 29 mg Cr(VI)/kg.
2	Human	once (IN)			7.5 M (death)	Kaufman et al. 1970	K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
3	Human	once (IN)			357 F (death)	Loubieres et al. 1999	CrO3 (VI)	35-year-old woman ingested chromic acid solution containing 25 g Cr(VI). Assuming 70 kg body weight, dose = 357 mg Cr(VI)/kg.
4	Human	once (IN)			4.1 M	Saryan and Reedy 1988	CrO3 (VI)	44-year-old man ingested ~2.8g Cr(VI) as chromium trioxide; ~4.1 mg Cr(VI)/kg body weight.
5	Rat (Fischer- 344) (G)	once			29 M (LD50) 25 F (LD50)	American Chrome and Chemicals 1989	CrO3 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
6	Rat (Fischer- 344) (GW)	once				21 M (LD50) 14 F (LD50)	Gad et al. 1986 Na2Cr2O7.2H2O (VI)	
7	Rat (Fischer- 344) (GW)	once				26 M (LD50) 17 F (LD50)	Gad et al. 1986 K2Cr2O7 (VI)	
8	Rat (Fischer- 344) (GW)	once				22 M (LD50) 19 F (LD50)	Gad et al. 1986 (NH4)2Cr2O7 (VI)	
9	Rat (Fischer- 344) (GW)	once				28 M (LD50) 13 F (LD50)	Gad et al. 1986 Na2CrO4 (VI)	
10	Rat Druckrey	2 wk (W)				89 F (15% mortality)	Kanojia et al. 1998 K2Cr2O7 (VI)	
11	Rat (NS)	once (G)				811 M (LD50)	Shubochkin and Pokhodzie 1980 SrCrO4 (VI)	
12	Rat (Sprague-Dawley)	once (G)				249 M (LD50) 108 F (LD50)	Vernot et al. 1977 CaCrO4 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic 13 Human	once (IN)	Resp			29 M (congested lungs, pleural effusions)	Clochesy 1984; Iserson et al. 1983 K2Cr2O7 (VI)	17-year-old, 60 kg boy ingested 5 g potassium dichromate [1,750 mg Cr(VI)]; dose = 29 mg Cr(VI)/kg.
		Cardio			29 M (hemorrhage, cardiac arrest)		
		Gastro			29 M (hemorrhage)		
		Hemato			29 M (inhibited coagulation)		
		Renal			29 M (necrosis swelling of renal tubules)		
14 Human	once (IN)	Dermal		0.04 M (enhancement of dermatitis)		Goltre et al. 1982 K2Cr2O7 (VI)	
15 Human	once (C)	Dermal		0.036 (dermatitis)		Kaaber and Veien 1977 K2Cr2O7 (VI)	

(continued)

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
16	Human	Gastro		7.5 M (abdominal pain and vomiting)		Kaufman et al. 1970 K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
17	Human	Hepatic			7.5 M (necrosis)		
		Gastro			357 F (intestinal hemorrhage and necrosis)	Loubieres et al. 1999 CrO3 (VI)	35-year-old woman ingested chromic acid solution containing 25 g Cr(VI). Assuming 70 kg body weight, dose = 357 mg Cr(VI)/kg.
		Hepatic			357 F (fatty degeneration)		
		Renal			357 F (acute renal failure and renal necrosis)		
		Metab			357 F (metabolic acidosis)		
18	Human	Gastro			4.1 M (gastrointestinal hemorrhage)	Saryan and Reedy 1988 CrO3 (VI)	44-year-old man ingested ~2.8g Cr(VI) as chromium trioxide; ~4.1 mg Cr(VI)/kg body weight.
		Renal			4.1 M (acute tubular necrosis)		

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
19	Rat (Fischer- 344) (W)	5 d	Hemato		4 M (decreased mean cell volume, mean cell hemoglobin, and reticulocyte count)		NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
20	Rat (Fischer- 344) (W)	4 d	Musc/skel	15.9 M	31.8 M (serum creatine kinase activity increased by 31%)		NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
				8.2 F				
					16.4 F (serum creatine kinase activity increased by 45%)			
21	Rat (NS)	once (G)	Hepatic		4 M (serum ALT activity increased by 15%)		Samitz 1970 K ₂ Cr ₂ O ₇ (VI)	
22	Rat (Fischer- 344) (W)	8 days	Hemato		2.8 M (decreased mean cell hemoglobin)		Thompson et al. 2012 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
23	Rat (NS)	once (G)	Renal				Thompson et al. 2012 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
24	Rat (NS)	once (G)	Gastro			130 (hemorrhage)	Thompson et al. 2012 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
25	Rat (Fischer- 344) (W)	8 days	Gastro		10 F (villous atrophy and crypt cell hyperplasia in duodenum and jejunum)		Thompson et al. 2012 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
23	Mouse (Swiss albino) 9 d Gd 6-14 (W)	Bd Wt	53.2 F	101.1 F (8.2% decrease in gestational weight gain)	152.4 F (24.3% decrease in gestational weight gain)	Junaïd et al. 1996b K2Cr2O7 (VI)	
24	Mouse (B6C3F1) 8 days (W)	Gastro	30 F			Thompson et al. 2011 Na2Cr2O7.2H2O (VI)	
Immuno/ Lymphoret							
25	Human once (IN)			0.04 M (enhancement of chromium dermatitis)		Goltre et al. 1982 K2Cr2O7 (VI)	
26	Human once (C)			0.036 (dermatitis)		Kaaber and Veien 1977 K2Cr2O7 (VI)	14-year-old boy ingested 1.5 g potassium dichromate [0.53 mg Cr(VI)]. Assuming 70 kg body weight, dose = 7.5 mg Cr(VI)/kg.
Neurological							
27	Human once (IN)				7.5 M (cerebral edema)	Kaufman et al. 1970 K2Cr2O7 (VI)	
Reproductive							
28	Rat (NS) 3 d Gd 1-3 (G)				35.7 F (preimplantation loss)	Bataineh et al. 2007 K2Cr2O7 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
29	Rat (NS)	3 d Gd 4-6 (G)			35.7 F (decreased number of viable fetuses; increased resorptions)	Bataineh et al. 2007 K2Cr2O7 (VI)	
30	Rat (Wistar)	6 d (G)			5.2 M (sperm count decreased by 76%, percentage of abnormal sperm increased by 143% and histopathological changes to seminiferous tubules)	Li et al. 2001 CrO3 (VI)	
31	Rat (Wistar)	10 d 1 x/d (G)			2.2 (20% lower final pups' body weight)	De Lucca et al. 2009 K2Cr2O7 (VI)	4.4 mg/kg/day decreased mandibular growth and delayed tooth eruption.
32	Rat (Wistar)	Gd 6-15 (W)			8 F (increased pre- and post-implantation loss, resorptions, dead fetuses/litter, skeletal and visceral malformations)	Elsaleed and Nada 2002 K2CrO4 (VI)	
33	Mouse (Swiss albino)	9 d Gd 6-14 (W)			53.2 F (increase in resorptions)	Junaied et al. 1996b K2Cr2O7 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure ^a (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE							
Death							
34	Mouse (Swiss albino) (W)				169 F (3/15 died)	Junaid et al. 1996a K2Cr2O7 (VI)	
Systemic							
35	Rat (Wistar)	Hepatic			1.3 M (increased serum ALT and AST and histopathological changes, including degeneration, vacuolization, increased sinusoidal space and necrosis)	Acharya et al. 2001 K2Cr2O2 (VI)	
Renal							
36	Rat (Sprague-Dawley)	Bd Wt		1.3 M (histopathological changes, including vacuolization in glomeruli, degeneration of basement membrane of Bowman's capsule and renal tubular epithelial degeneration)	42 M (19% lower final body weight)	Bataineh et al. 1997 K2Cr2O7 (VI)	
37	Rat Charles Foster	Bd Wt	20 M		40 M (57% decreased body weight)	Chowdhury and Mitra 1995 Na2Cr2O7 (VI)	
38	Rat (Wistar)	Renal	10 M		100 M (proteinuria, oliguria)	Diaz-Mayans et al. 1986 Na2CrO4 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
39	Rat Swiss albino 20 d (W)	Bd Wt	37	70 (14% reduced maternal body weight gain)	87 (21% reduced maternal body weight gain)	Kanojia et al. 1996 K2Cr2O7 (VI)	
40	Rat Druckrey 3 mo (W)	Bd Wt	45	89 (18% reduced maternal body weight gain)	124 (24% reduced maternal body weight gain)	Kanojia et al. 1998 K2Cr2O7 (VI)	
41	Rat (albino) 20 d 7 d/wk (G)	Hepatic		13.5 M (lipid accumulation)		Kumar and Rana 1982 K2CrO4 (VI)	
		Renal		13.5 M (lipid accumulation)			
42	Rat (white) 20 d 7 d/wk (G)	Renal		13.5 M (inhibition of membrane enzymes; alkaline phosphatase, acid phosphatase, lipase)		Kumar and Rana 1984 K2CrO4 (VI)	
43	Rat (albino) 20 d 7 d/wk (G)	Hepatic		13.5 M (changes in liver enzyme activities; inhibition of acid phosphatase; enhancement of lipase)		Kumar et al. 1985 K2CrO4 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
44	Rat (Sprague- Dawley)	9 wk (F)	Hemato	2.1 M	8.4 M		NTP 1996b K2Cr2O7 (VI)	
				2.5 F	9.8 F (decreased mean corpuscular volume)			
			Hepatic	9.8				
			Renal	9.8				
			Bd Wt	9.8				

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
45	Rat (Fischer- 344) (W)	14 wk	Resp	20.9			NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
			Cardio	20.9				
			Gastro	1.7	3.5 (duodenal histiocytic cellular infiltration)			
			Hemato		1.7 (microcytic, hypochromic anemia)			
			Musc/skel	3.5	5.9 (serum creatine kinase activity increased by 31% in males and 45% in females)			
			Hepatic		1.7 (serum ALT activity increased by 14% in males 30% in females, serum SDH activity increased by 77% in males and 359% in females)			
			Renal	20.9				
			Endocr	20.9				
			Ocular	20.9				
			Bd Wt	5.9 M	11.2 M (11% decrease in body weight)			

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
46	Rat (Fischer- 344) (W)	23 d	Hemato		1.7 M (decreased hematocrit, mean cell volume, mean hemoglobin concentration, reticulocyte)		NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
					1.7 F (decreased hemoglobin and mean cell volume)			
47	Rat (Fischer- 344) (W)	6 mo	Hemato	0.21 M	0.77 M (microcytic, hypochromic anemia)		NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
48	Rat (Fischer- 344) (W)	22 d	Hemato	0.21 M	^b 0.77 M (microcytic, hypochromic anemia)		NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
49	Rat (Wistar)	30 d	Endocr		73 M (59% decrease in serum prolactin)		Quinteros et al. 2007 K ₂ Cr ₂ O ₇ (VI)	
			Bd Wt		73 M (11.6% in body weight)			

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
50	Rat (Wistar)	Hepatic			3.7 M (serum ALT activity increased by 253%, histopathological changes including focal necrosis and degeneration with changes in vascularization)	Rafael et al. 2007 Cr (VI)	
		Metab		3.7 M (65% increase in serum glucose)			
51	Rat (Wistar)	Renal		3.4 F (decreased creatinine clearance, increased plasma creatinine, urea, and uric acid; proximal tubule necrosis, intraglomerular hemorrhage)		Soudani et al. 2010a K2Cr2O7 (VI)	
52	Rat (Wistar)	Renal			9.4 F (kidney hemorrhage and necrosis)	Soudani et al. 2010b K2Cr2O7 (VI)	
		Bd Wt	9.4 F				

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
53	Rat (Wistar) 21 d Gd 14-21 Ld 1-14 ad lib (W)	Hepatic			9.4 F (liver necrosis)	Soudani et al. 2011a K2Cr2O7 (VI)	Antioxidant enzyme activities were reduced in the liver.
		Bd Wt	9.4 F				
54	Rat (Wistar) 3 wk ad lib (W)	Cardio			26 F (heart hemorrhage and necrosis)	Soudani et al. 2011c K2Cr2O7 (VI)	Chromium caused oxidative stress in heart tissue.
55	Rat (Fischer- 344) (W) 91 days	Gastro	0.21 F	2.9 F (histiocytic infiltration in the duodenum villi)		Thompson et al. 2012 Na2Cr2O7.2H2O (VI)	
		Hemato	2.9 F	7.1 F (decreased serum and bone marrow iron levels)			
56	Mouse BDF1 210 d (W)	Bd Wt	1.4 F	14 F (13.5% decrease in body weight gain)		De Flora et al. 2006 Na2Cr2O7.2H2O (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)			
57	Mouse (BALB/c)	Hemato	9 wk (F)					
				7.4 M	32.2 M		NTP 1996a	
		Hepatic		12 F	48 F (decreased mean corpuscular volume)		K2Cr2O7 (VI)	
				1.1 M	3.5 M			
58	Mouse (BALB/c)	Renal		1.8 F	5.6 F (cytoplasmic vacuolization of hepatocytes)			
				48				
		Bd Wt		48				
		Gastro		36.7 F			NTP 1997	
			85 d + pnd 1-74 (F1) + pnd 1-21 (F2) (F)				K2Cr2O7 (VI)	
		Hemato			7.8 F (decreased mean corpuscular volume in F1)			
		Hepatic		36.7 F				
		Renal		36.7 F				
		Bd Wt		36.7 F				

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
59	Mouse (B6C3F1)	14 wk (W)	Resp	27.9			NTP 2007 Na2Cr2O7.2H2O (VI)	
			Cardio	27.9				
			Gastro		3.1 (epithelial hyperplasia of duodenum)			
			Hemato		3.1 M (decreased mean cell volume)			
					3.1 F (decreased mean cell hemoglobin)			
			Hepatic	27.9				
			Renal	27.9				
60	Mouse (B6C3F1)	22 d (W)	Endocr	27.9			NTP 2008a Na2Cr2O7.2H2O (VI)	
			Ocular	27.9				
			Bd Wt	3.1 F	3.1 M (6% decrease in body weight)			
					5.2 F (8% decrease in body weight)			
			Hemato		0.38 F (microcytic, hypochromic anemia and increased lymphocytes)			

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
61	Mouse (B6C3F1)	6 mo (W)	Hemato	0.38 F	1.4 F (decreased mean cell volume)	NTP 2008a Na2Cr2O7.2H2O (VI)	
62	Mouse (B6C3F1)	91 days (W)	Gastro	1.1 F	4.6 F (villous cytoplasmic vacuolization in duodenum and jejunum)	Thompson et al. 2011 Na2Cr2O7.2H2O (VI)	
63	Mouse (albino)	19 d (W)	Hemato	31 F			
			Bd Wt	46 F	98 F (decreased maternal weight gain)	Trivedi et al. 1989 K2Cr2O7 (VI)	
64	Rabbit (New Zealand)	daily 10 wk (G)	Bd Wt	3.6 M		Yousef et al. 2006 K2Cr2O7 (VI)	
Immunol/ Lymphoret							
65	Rat (Fischer- 344)	14 wk (W)		11.2 F	1.7 M (histiocytic cellular infiltration of pancreatic lymph nodes)	NTP 2007 Na2Cr2O7.2H2O (VI)	
					20.9 F (histiocytic cellular infiltration of pancreatic lymph nodes)		

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
66	Rat (Fischer- 344) (W)	3-10 wk			16 (increased proliferation of T- and B- lymphocytes in response to mitogens and antigens)		Snyder and Valle 1991 K ₂ CrO ₄ (VI)	
67	Mouse (B6C3F1)	14 wk (W)			3.1 (histiocytic infiltrate of mesenteric lymph nodes)		NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
Neurological								
68	Rat (Wistar)	28 d (W)		10 M	100 M (decreased motor activity)		Diaz-Mayans et al. 1986 Na ₂ CrO ₄ (VI)	
69	Rat (Fischer- 344) (W)	14 wk		20.9			NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
70	Mouse (B6C3F1)	14 wk (W)		27.9			NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	LOAEL				Reference	Comments
			System	NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Reproductive								
71	Monkey macaca	180 d (W)				2.1 M (histopathological changes to epididymides, including ductal obstruction and development of microcanals)	Aruldas et al. 2004 K2Cr2O7 (VI)	
72	Monkey macaca	180 d (W)				2.1 M (decreased testes weight, histopathological changes including depletion of germ cells, hyperplasia of Leydig cells, disrupted spermatogenesis, Sertoli cell fibrosis, alterations of sperm morphology)	Aruldas et al. 2005 K2Cr2O7 (VI)	
73	Monkey macaca	180 d (W)				2.1 M (histopathological changes to basal cells and principal cells of epididymis)	Aruldas et al. 2006 K2Cr2O7 (VI)	
74	Monkey macaca	180 d (W)		1.1 M		2.1 M (sperm count and motility decreased by 25%)	Subramanian et al. 2006 K2Cr2O7 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
75	Rat (Sprague-Dawley)	12 wk (W)			42 (altered sexual behavior, decreased absolute testes, seminal vesicles, and preputial gland weights)		Bataineh et al. 1997 K2Cr2O7 (VI)	
76	Rat (Charles Foster)	90 d 1 x/d (G)			20 M (decreased testicular protein, 3 beta-hydroxy steroid dehydrogenase and serum testosterone)	40 M (28% decreased testicular weight; decreased testicular protein, DNA, RNA, seminiferous tubular diameter; decreased Leydig cells, pachytene cells, spermatocytes, spermatids, and testosterone levels)	Chowdhury and Mitra 1995 Na2Cr2O7 (VI)	
77	Rat Swiss albino	20 d (W)				37 (increased resorptions)	Kanojia et al. 1996 K2Cr2O7 (VI)	
78	Rat Druckrey	3 mo (W)				45 (decreased fertility, increased pre- and post-implantation loss)	Kanojia et al. 1998 K2Cr2O7 (VI)	
79	Rat (Sprague-Dawley)	9 wk (F)		8.4 M 9.8 F			NTP 1996b K2Cr2O7 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)			
80	Rat (Fischer- 344) (W)	14 wk	20.9				NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
81	Mouse (Swiss albino) (W)	20 d		52 F (decreased placental weight)	98 F (preimplantation loss, increased resorptions)		Junaid et al. 1996a K ₂ Cr ₂ O ₇ (VI)	
82	Mouse Swiss albino (W)	20 d		60 F (decreased number of follicles at different stages of maturation)	120 F (decreased number of ova/mouse)		Murthy et al. 1996 K ₂ Cr ₂ O ₇ (VI)	
83	Mouse (BALB/c)	9 wk (F)	32.2 M 48 F				NTP 1996a K ₂ Cr ₂ O ₇ (VI)	
84	Mouse (BALB/c)	85 d + pnd 1-74 (F1) + pnd 1-21(F2) (F)	36.7 F				NTP 1997 K ₂ Cr ₂ O ₇ (VI)	
85	Mouse (B6C3F1)	14 wk (W)	27.9				NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
86	Mouse (B6C3F1)	14 wk (W)	8.7 M				NTP 2007 Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
87	Mouse (albino)	Gd 1-19 19 d (W)			46 F (increase in fetal resorption and post implantation loss)	Trivedi et al. 1989 K2Cr2O7 (VI)	
88	Mouse (BALB/c)	7 wk 7 d/wk (F)			15.2 M (decreased spermatogenesis)	Zahid et al. 1990 K2Cr2O7 (VI)	
89	Rabbit (New Zealand)	daily 10 wk (G)			2.6 M (plasma testosterone decreased by 20.8%, sperm count decreased by 18%, % dead sperm increased by 23.9%, total mobile sperm decreased by 34.3%)	Yousef et al. 2006 K2Cr2O7 (VI)	
Developmental 90	Rat (Wistar)	Ld 1-21 (W)		11.4 F (delayed follicular development and pubertal onset)		Banu et al. 2008 K2Cr2O7 (VI)	Chromium also impaired ovarian steroidogenesis.
91	Rat Swiss albino	20 d (W)			37 (increased post-implantation loss and decreased number of live fetuses)	Kanojia et al. 1996 K2Cr2O7 (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
92	Rat Druckrey	3 mo (W)			45 (reduced fetal caudal ossification, increased post-implantation loss, reduced fetal weight, subhemorrhagic patches)	Kanojia et al. 1998 K2Cr2O7 (VI)	
93	Rat (Wistar)	21 d Ld 1-21 (W)		2.9 F (13% reduced pup's by weight; delayed onset of puberty)	11.4 F (26-33% reduced final pup's body weight)	Samuel et al. 2011 K2Cr2O7 (VI)	2.9 mg/kg/day also decreased steroid hormones in serum and increased free radicals in uterus).
94	Rat (Wistar)	21 d Gd 14-21 Pnd 1-14 ad lib (W)			9.4 (26% reduced pup's body weight; kidney hemorrhage)	Soudani et al. 2010b K2Cr2O7 (VI)	
95	Rat (Wistar)	21 d Gd 14-21 Ld 1-14 ad lib (W)			9.4 (26% reduced pup's weight on Pnd 14)	Soudani et al. 2011a K2Cr2O7 (VI)	Antioxidant enzyme activities were reduced in pup's liver.
96	Rat (Wistar)	21 d Gd 14-21 Ld 1-14 ad lib (W)			9.4 (25% reduced final pup's body weight)	Soudani et al. 2011b K2Cr2O7 (VI)	Antioxidant enzymes were decreased in bone; bone resorption was increased.

(continued)

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
97	Mouse (BALB/c)	Gd 12- Ld 20 (W)		66 F (delayed time of vaginal opening and impaired fertility in female offspring)		Al-Hamood et al. 1998 K2Cr2O7 (VI)	
98	Mouse BDF1	Gd 0-18 (W)	4.8 F			De Flora et al. 2006 Na2Cr2O7.2H2O (VI)	
99	Mouse BDF1	Gd 0-18 (W)	2.4 F			De Flora et al. 2006 K2Cr2O7 (VI)	
100	Mouse (Swiss albino) (W)	20 d			52 F (reduced caudal ossification in fetuses; decreased fetal weight; post-implantation loss)	Junaaid et al. 1996a K2Cr2O7 (VI)	
101	Mouse (albino)	Gd 1-19 19 d (W)			46 (increased resorptions, reduced ossification, gross anomalies)	Trivedi et al. 1989 K2Cr2O7 (VI)	
CHRONIC EXPOSURE							
Death							
102	Rat (Fischer- 344) (W)	2 yr	7 F			NTP 2008a Na2Cr2O7.2H2O (VI)	

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/ Frequency (Route)	LOAEL				Reference	Comments
			System	NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
103	Mouse (B6C3F1)	2 yr (W)		8.7 F			NTP 2008a	
Systemic								
104	Human	NS (environ)	Gastro		0.57 (oral ulcer, diarrhea, abdominal pain, indigestion, vomiting)		Zhang and Li 1987 (VI)	Exposed to well water containing 20 mg Cr(VI)/L; assuming 70 kg body weight and drinking water consumption of 2 L/day, dose = 0.57 mg Cr(VI)/kg/day.
105	Rat (Sprague-Dawley)	1 yr (W)	Hemato	3.6			Mackenzie et al. 1958 K2CrO4 (VI)	
			Hepatic	3.6				
			Renal	3.6				
			Bd Wt	3.6				
106	Rat (Fischer- 344)	12 mo (W)	Hemato	0.21 M	0.77 M (decreased mean cell hemoglobin)		NTP 2008a	
			Musc/skel	0.94 M	2.4 M (creatine kinase activity increased by 64%)		Na2Cr2O7.2H2O (VI)	
			Hepatic	0.21 M	0.77 M (serum ALT increased by 156%)			

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
107	Rat (Fischer- 344) (W)	2 yr	Resp	7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
			Cardio	7 F				
			Gastro	0.21 M	0.77 M (histiocytic cellular infiltration of duodenum)			
				0.94 F				
			Hepatic		2.4 F (histiocytic cellular infiltrate of duodenum)			
				0.21 M	0.77 M (basophilic foci of liver)			
108	Mouse (B6C3F1)	1 yr (W)	Renal	7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
			Endocr	7 F				
			Ocular	7 F				
			Bd Wt	2.1 M	5.9 M (12% decrease in body weight)			
				1.4 F	3.1 F (increased RBC count, decreased mean cell volume and mean cell hemoglobin)			

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
109 Mouse (B6C3F1)	2 yr (W)	Resp	8.7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
		Cardio	8.7 F				
		Gastro		0.38 ^C	(epithelial hyperplasia of duodenum in males and female and cytoplasmic alteration of pancreas in females)		
		Hepatic	2.4 M	5.9 M	(clear cell and eosinophilic foci)		
Immuno/ Lymphoret 110 Rat (Fischer- 344) (W)	2 yr	Renal	8.7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
		Endocr	8.7 F				
		Ocular	8.7 F				
			0.21 M	0.77 M	(histiocytic cellular infiltration and hemorrhage of mesenteric nodes)		
			0.94 F				
				2.4 F	(histiocytic cellular infiltration of mesenteric and pancreatic nodes)		

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
111	Mouse (B6C3F1)	2 yr (W)		0.38	(histiocytic cellular infiltration of mesenteric lymph nodes)	NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
Neurological							
112	Rat (Fischer- 344) (W)	2 yr (W)	7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
113	Mouse (B6C3F1)	2 yr (W)	8.7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
Reproductive							
114	Rat (Fischer- 344) (W)	2 yr (W)	6.6 M 7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
115	Mouse (B6C3F1)	2 yr (W)	5.9 M 8.7 F			NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	

Table 3-4 Levels of Significant Exposure to Chromium VI - Oral (continued)

Key to Species Figure (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer							
116 Human	(environ)				0.57 (CEL: lung and stomach cancer)	Zhang and Li 1987 Cr (VI)	Exposed to well water containing 20 mg Cr(VI)/L; assuming 70 kg body weight and drinking water consumption of 2 L/day, dose = 0.57 mg Cr(VI)/kg/day.
117 Rat (Fischer- 344) (W)	2 yr				5.9 M (CEL: neoplasm of squamous epithelium of mouth and tongue)	NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
					7 F (CEL: neoplasm of squamous cell epithelium of mouth and tongue)		
118 Mouse (B6C3F1) (W)	2 yr				3.1 M (CEL: neoplastic lesions of small intestine)	NTP 2008a Na ₂ Cr ₂ O ₇ ·2H ₂ O (VI)	
					2.4 M (CEL: neoplastic lesions of small intestine)		

a The number corresponds to entries in Figure 3-3.

b Used to derive an intermediate-duration oral MRL of 0.005 mg chromium(VI)/kg/day for hexavalent chromium compounds. Benchmark dose of 0.52 mg chromium(VI)/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

c Used to derive a chronic-duration oral MRL of 0.0009 mg chromium(VI)/kg/day for hexavalent chromium compounds. Benchmark dose of 0.09 mg chromium(VI)/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; environ = environmental; (F) = feed; F = female; F1 = first generation; F2 = second generation; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunologically/lymphoreticular; (IN) = ingestion; Ld = lactational day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post natal day; RBC = red blood cell; Resp = respiratory; (W) = drinking water; wk = week(s); x = times; yr = year(s)

Acute (≤ 14 days)



Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral (Continued)

Acute (≤14 days)

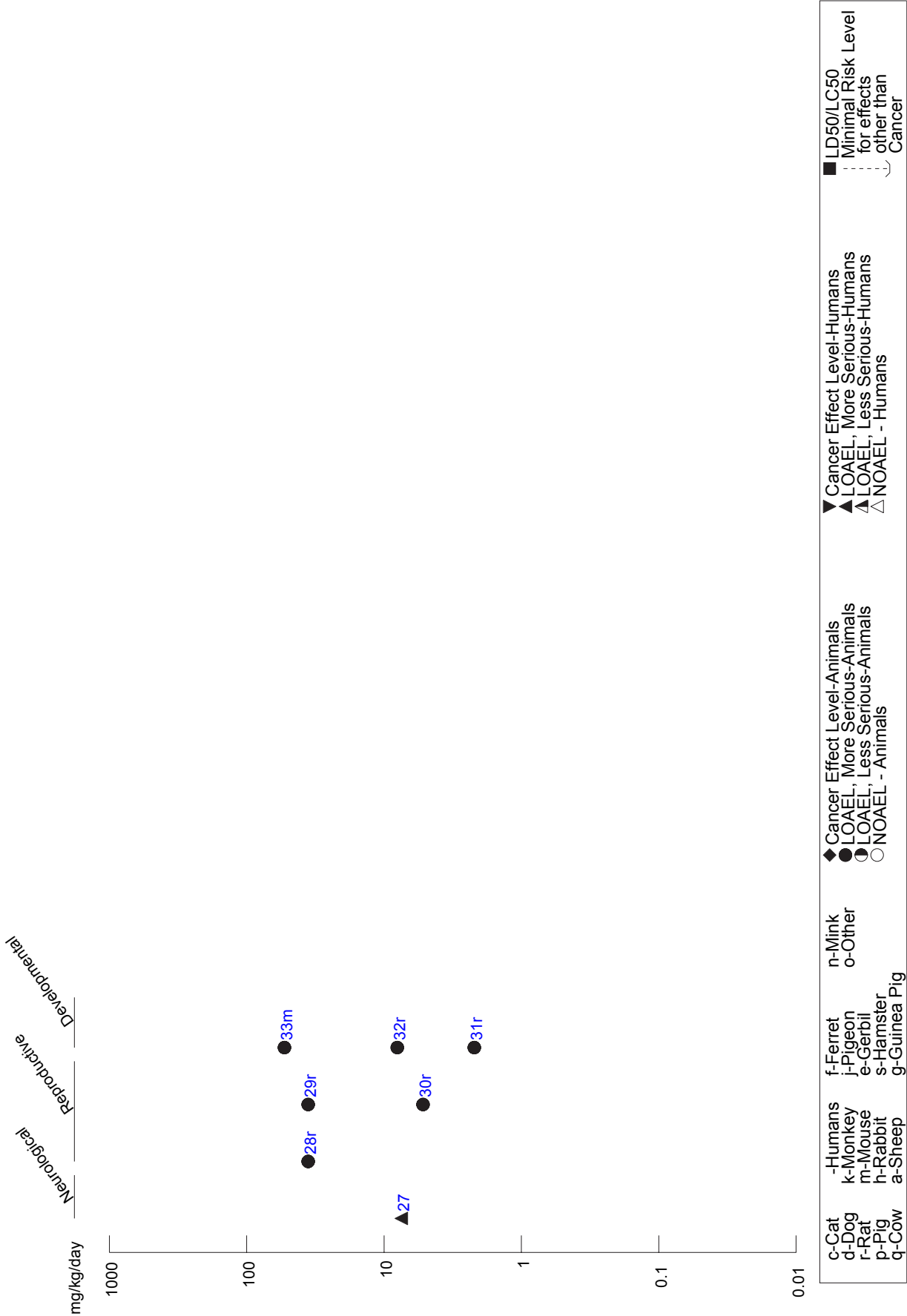
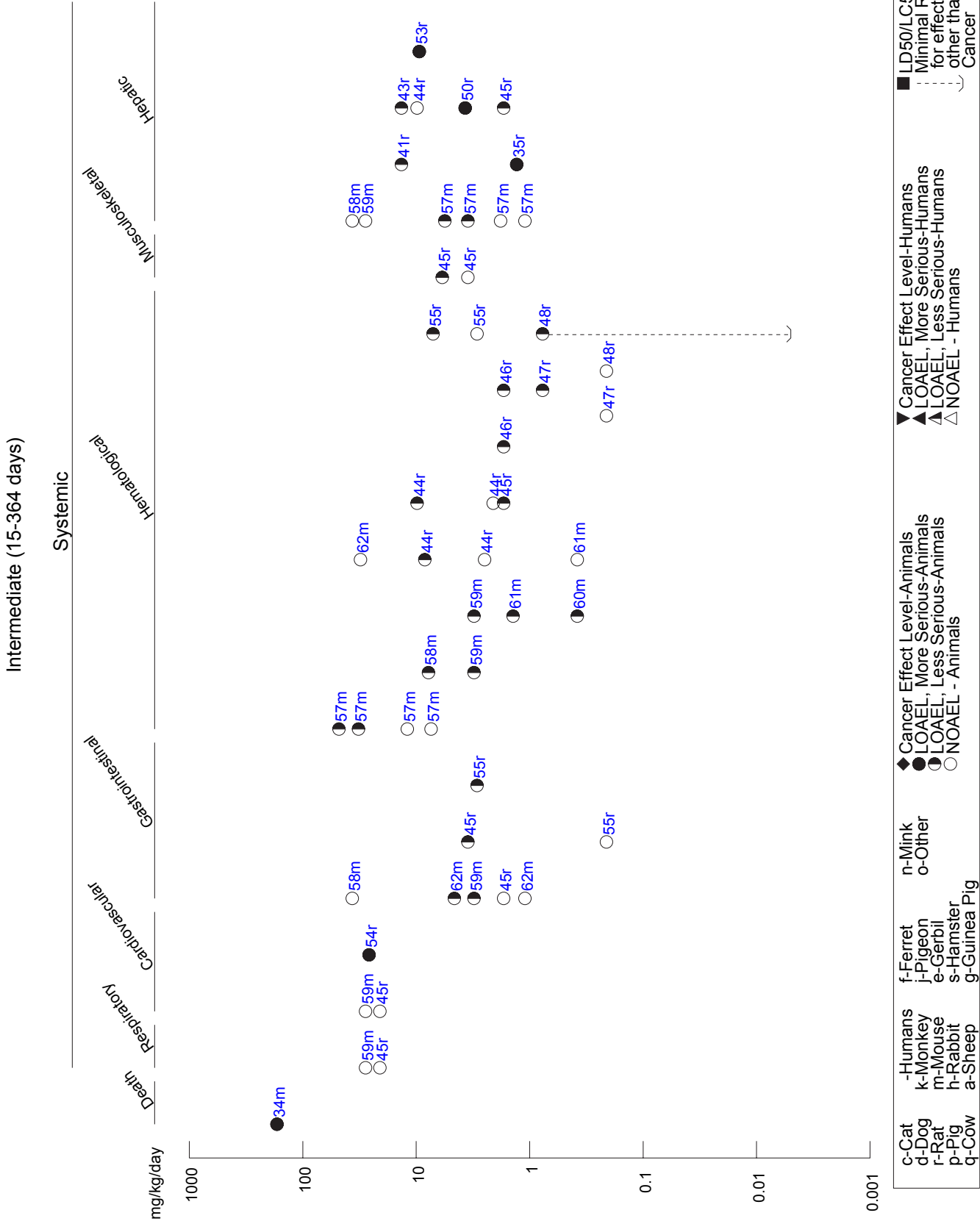


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral (Continued)



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Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral (Continued)

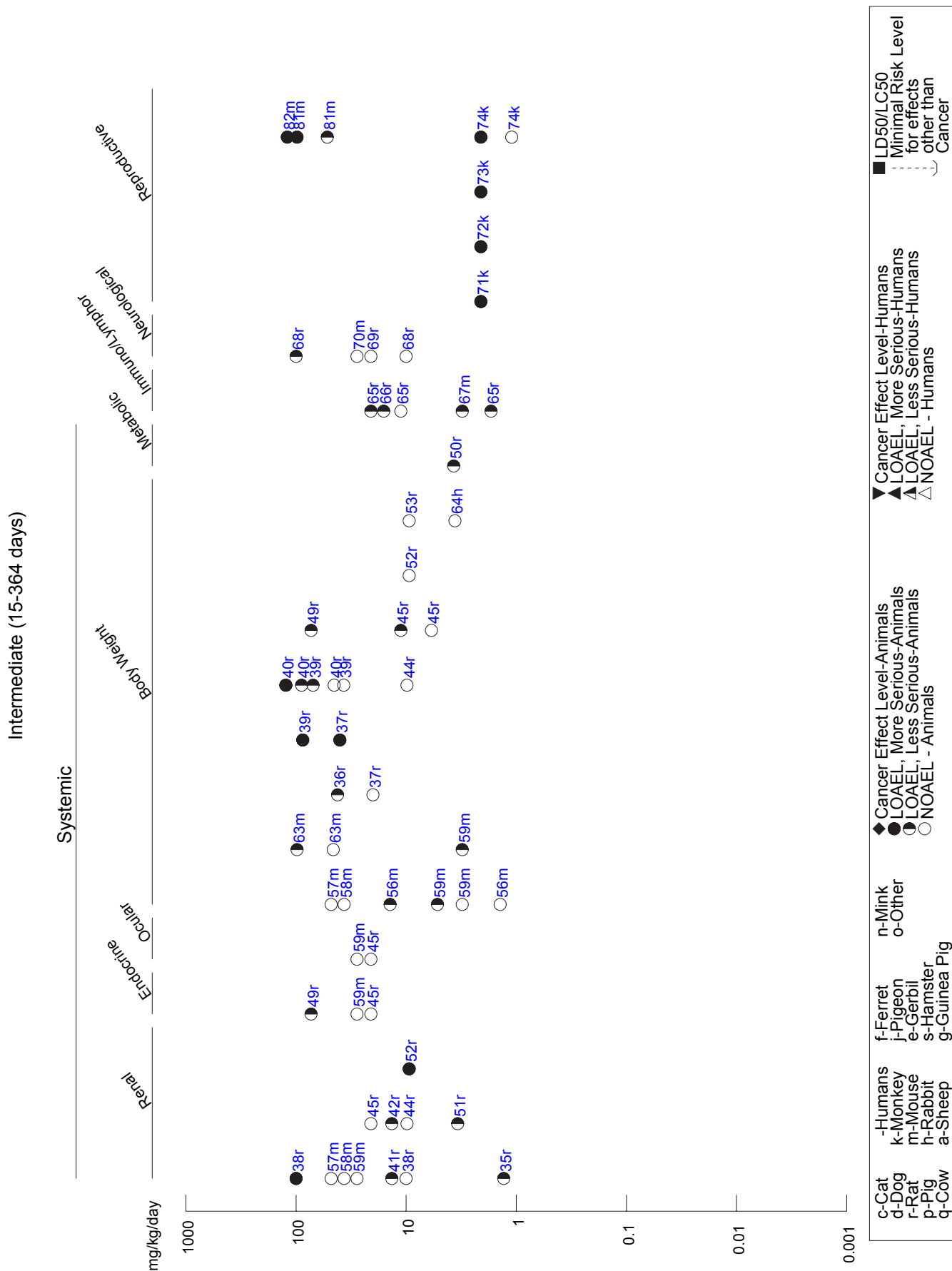


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral (Continued)

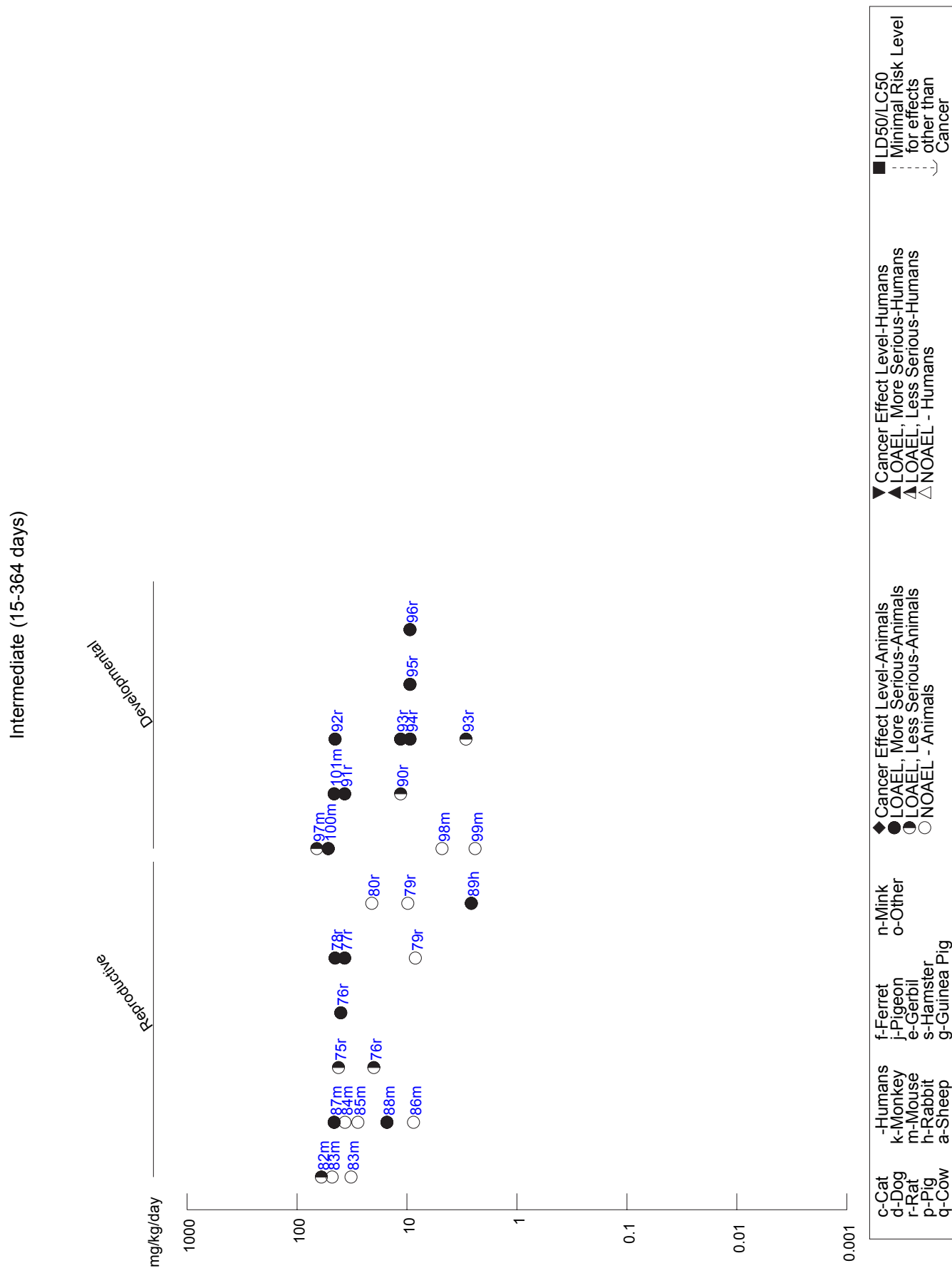


Figure 3-3 Levels of Significant Exposure to Chromium VI - Oral (Continued)

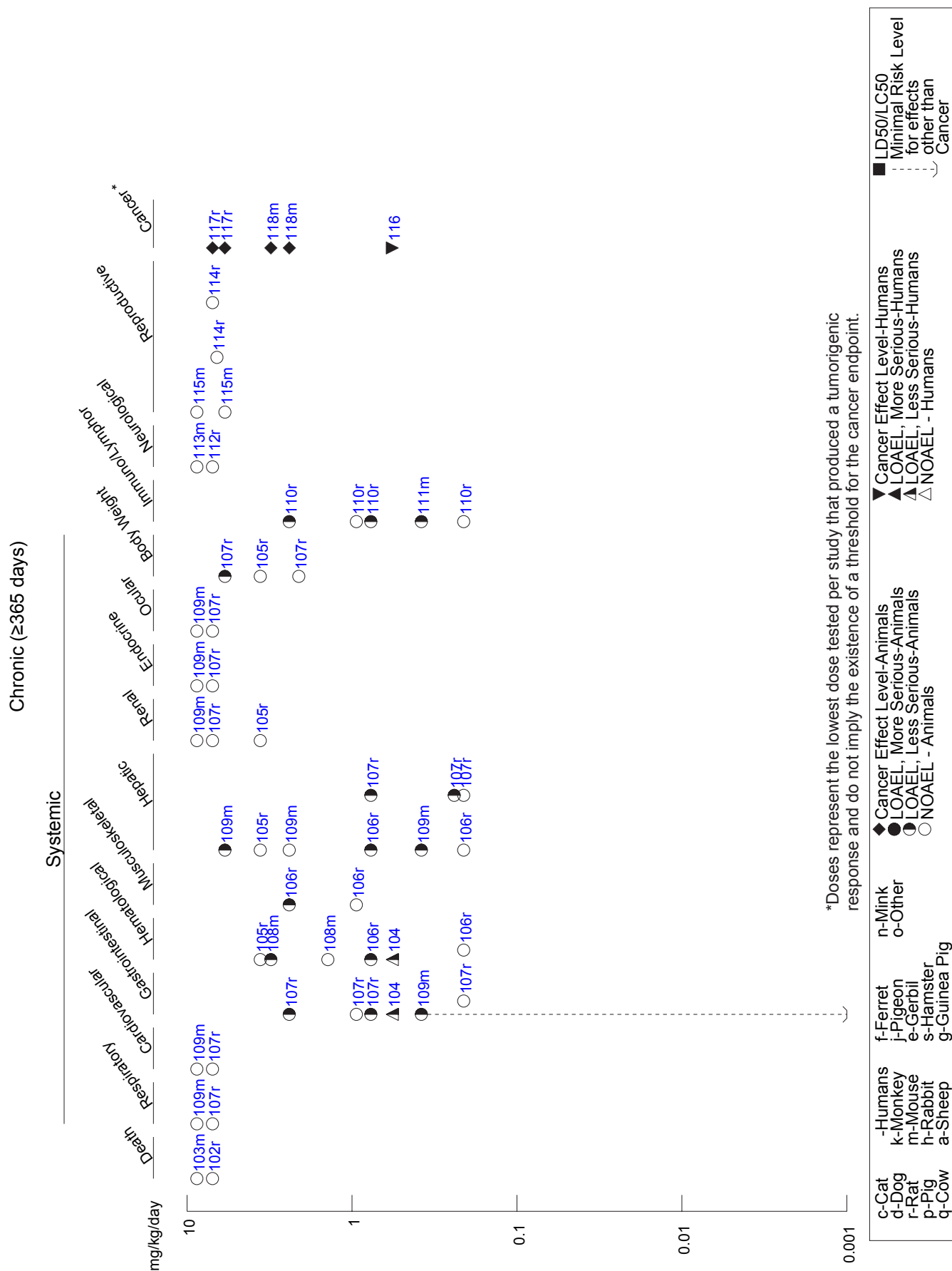


Table 3-5 Levels of Significant Exposure to Chromium III - Oral

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE							
Death							
1	Rat (NS) once (GW)				2365 (LD50)	Smyth et al. 1969 Cr(CH3COO)3H2O (III)	
2	Rat (Sprague-Dawley) once (G)				200 M (LD50) 183 F (LD50)	Vernot et al. 1977 Cr(NO3)3.9H2O (III)	
Systemic							
3	Rat (Fischer- 344) (F) 3 d	Hemato	506 F			NTP 2008b Cr picolinate (III)	
Reproductive							
4	Rat (NS) 3 d Gd 1-3 (G)				33.6 F (decreased number of pregnancies)	Bataineh et al. 2007 CrCl3 (III)	
5	Rat (NS) 3 d Gd 4-6 (G)		33.6 F			Bataineh et al. 2007 CrCl3 (III)	
Developmental							
6	Mouse (CD-1) 11 d Gd 6-17 1 x/d (F)		25			Bailey et al. 2008a Cr picolinate (III)	NOAEL is for standard developmental end points.
INTERMEDIATE EXPOSURE							
Systemic							
7	Rat (Sprague-Dawley) daily 20 wk (F)	Hepatic	9			Anderson et al. 1997b CrCl3 (III)	
		Renal	9				
		Bd Wt	9				

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
8	Rat (Sprague-Dawley)	daily 20 wk (F)	Hepatic	9				Anderson et al. 1997b Cr picolinate (III)	
			Renal	9					
			Bd Wt	9					
9	Rat (Sprague-Dawley)	12 wk (W)	Bd Wt			40	(24% lower final body weight)	Bataineh et al. 1997 CrCl3 (III)	
10	Rat (BD)	90 d 5 d/wk (F)	Resp	1806				Ivankovic and Preussmann 1975 Cr2O3 (III)	
			Cardio	1806					
			Gastro	1806					
			Hemato	1806					
			Hepatic	1806					
			Renal	1806					

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
11	Rat (Fischer- 344) (F)	14 wk	Resp	506 F			NTP 2008b Cr picolinate (III)	
			Cardio	506 F				
			Gastro	506 F				
			Hemato	506 F				
			Hepatic	506 F				
			Renal	506 F				
			Endocr	506 F				
			Ocular	506 F				
			Bd Wt	506 F				
12	Rat (Sprague-Dawley)	90 d (F)	Resp	1.5 F			Shara et al. 2005 Cr nicotinate (III)	
			Cardio	1.5 F				
			Gastro	1.5 F				
			Hemato	1.5 F				
			Hepatic	1.5 F				
			Renal	1.5 F				
			Endocr	1.5 F				
			Bd Wt	1.5 F				

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
13	Rat (Sprague-Dawley)	38 wk (F)	Resp	0.25 F			Shara et al. 2007 Cr nicotinate (III)	
			Cardio	0.25 F			De Flora et al. 2006 CrK(SO ₄) ₂ (III)	
			Gastro	0.25 F				
			Hemato	0.25 F				
			Hepatic	0.25 F				
			Renal	0.25 F			De Flora et al. 2006 CrK(SO ₄) ₂ (III)	
			Endocr	0.25 F				
14	Mouse BDF1	210 d (W)	Bd Wt	165 M			Elbetieha and Al-Hamood 1997 CrCl ₃ (III)	
				140 F				
15	Mouse (Swiss)	12 wk (W)	Bd Wt	14 F	5 M (14% decrease in body weight gain)			

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)		
16	Mouse (B6C3F1)	14 wk (F)	1415 M			NTP 2008b Cr picolinate (III)	
		Resp					
		Cardio	1415 M				
		Gastro	1415 M				
		Hemato	1415 M				
		Hepatic	1415 M				
		Renal	1415 M				
		Endocr	1415 M				
		Ocular	1415 M				
		Bd Wt	1415 M				
Immuno/ Lymphoret							
17	Rat (Fischer- 344) (F)	14 wk	506 F			NTP 2008b Cr picolinate (III)	
18	Rat (Sprague- Dawley)	90 d (F)	1.5 F			Shara et al. 2005 Cr nicotinate (III)	
19	Rat (Sprague- Dawley)	38 wk (F)	0.25 F			Shara et al. 2007 Cr nicotinate (III)	
20	Mouse (B6C3F1)	14 wk (F)	1415 M			NTP 2008b Cr picolinate (III)	
Neurological							
21	Rat	90 d 5 d/wk (F)	1806			Ivankovic and Preussmann 1975 Cr III	

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
22	Rat (Fischer- 344) (F)	14 wk		506 F				NTP 2008b Cr picolinate (III)	
23	Rat (Fischer- 344) ad lib (F)	14 wk		506 F				NTP 2008b Cr picolinate (III)	
24	Rat (Sprague-Dawley)	90 d (F)		1.5 F				Shara et al. 2005 Cr nicotinate (III)	
25	Rat (Sprague-Dawley)	38 wk (F)		0.25 F				Shara et al. 2007 Cr nicotinate (III)	
26	Mouse (B6C3F1) (F)	14 wk ad lib (F)		1415 M				NTP 2008b Cr picolinate (III)	
Reproductive									
27	Rat (Sprague-Dawley)	12 wk (W)			40 (altered sexual behavior, decreased absolute testes, seminal vesicles, and preputial gland weights)			Bataineh et al. 1997 CrCl3 (III)	
28	Rat (Fischer- 344) (F)	14 wk		506 F				NTP 2008b Cr picolinate (III)	
29	Rat (Sprague-Dawley)	90 d (F)		1.5 F				Shara et al. 2005 Cr nicotinate (III)	

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)			
30	Rat (Sprague- Dawley)	38 wk (F)	0.25 F				Shara et al. 2007 Cr nicotinate (III)	
31	Mouse (Swiss)	12 wk (W)		5 M (increased testes and decreased preputial gland weights)	5 F (decreased number of implantations and viable fetuses; increased ovarian and decreased uterine weights)		Elbetieha and Al-Hamood 1997 CrCl3 (III)	
32	Mouse (B6C3F1)	14 wk (F)	1415 M				NTP 2008b Cr picolinate (III)	
33	Mouse (BALB/c)	7 wk 7 d/wk (F)			9.1 M (decreased spermatogenesis)		Zahid et al. 1990 Cr2(SO4)3 (III)	
Developmental								
34	Rat (BD)	90 d 5 d/wk (F)	1806				Ivankovic and Preussmann 1975 Cr2O3 (III)	
35	Mouse (BALB/c)	Gd 12- Ld 20 (W)		74 (reduced ovary and testis weights in offspring and impaired fertility in female offspring)			Al-Hamood et al. 1998 CrCl3 (III)	

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
36	Mouse (CD-1)	Gd 6-21 Ld 1-21 ad lib (F)		25			Bailey et al. 2008b Cr picolinate (III)	NOAEL is for standard neurodevelopmental end points.
CHRONIC EXPOSURE								
Systemic								
37	Rat (BD)	2 yr 5 d/wk (F)	Resp	2040			Ivankovic and Preussmann 1975 Cr2O3 (III)	
			Cardio	2040				
			Gastro	2040				
			Hepatic	2040				
			Renal	2040				
38	Rat (Sprague-Dawley)	1 yr (W)	Hemato	3.6			Mackenzie et al. 1958 CrCl3 (III)	
			Hepatic	3.6				
			Renal	3.6				
			Bd Wt	3.6				

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
39	Rat (Fischer- 344) (F)	2 yr	Resp	313 F			NTP 2008b Cr picolinate (III)	
			Cardio	313 F				
			Gastro	313 F				
			Hepatic	313 F				
			Renal	313 F				
			Endocr	313 F				
			Ocular	313 F				
			Bd Wt	313 F				
40	Rat (Long- Evans) 7 d/wk (W)	2-3 yr	Cardio	0.46			Schroeder et al. 1965 Cr(CH ₃ COO) ₃ (III)	
			Hepatic	0.46				
			Renal	0.46				
			Bd Wt	0.46				

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
41	Rat (Sprague-Dawley)	52 wk (F)	Resp	0.25 F			Shara et al. 2007 Cr nicotine (III)	
42	Mouse (B6C3F1)	2 yr (F)	Resp	781 M			NTP 2008b Cr picolinate (III)	
			Cardio	781 M				
			Gastro	781 M				
			Hepatic	781 M				
			Renal	781 M				
			Endocr	781 M				
			Ocular	781 M				
			Bd Wt	781 M				

0.22 M (14.9% decrease in body weight)

0.25 F (9.6% decrease in body weight)

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		
Immuno/ Lymphoret						
43	Rat (Fischer- 344) (F)		313 F		NTP 2008b Cr picolinate (III)	
44	Rat (Sprague- Dawley) (F)		0.25 F		Shara et al. 2007 Cr nicotinate (III)	
45	Mouse (B6C3F1) (F)		781 M		NTP 2008b Cr picolinate (III)	
Neurological						
46	Rat 2 yr 5 d/wk (F)		2040		Ivankovic and Preussmann 1975 Cr III	
47	Rat (Fischer- 344) (F)		313 F		NTP 2008b Cr picolinate (III)	
48	Rat (Sprague- Dawley) (F)		0.25 F		Shara et al. 2007 Cr nicotinate (III)	
49	Mouse (B6C3F1) (F)		781 M		NTP 2008b Cr picolinate (III)	
Reproductive						
50	Rat (Fischer- 344) (F)		313 F		NTP 2008b Cr picolinate (III)	
51	Rat (Sprague- Dawley) (F)		0.25 F		Shara et al. 2007 Cr nicotinate (III)	

Table 3-5 Levels of Significant Exposure to Chromium III - Oral (continued)

Key to Species Figure (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form	Comments
				Less Serious (mg/kg/day)	Serious (mg/kg/day)			
52	Mouse (B6C3F1)	2 yr (F)	781 M				NTP 2008b Cr picolinate (III)	
Cancer								
53	Rat (Fischer- 344) (F)	2 yr			55 M (equivocal evidence for prepubital gland adenoma)		NTP 2008b Cr picolinate (III)	

a The number corresponds to entries in Figure 3-4.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-4 Levels of Significant Exposure to Chromium III - Oral

Acute (≤14 days)

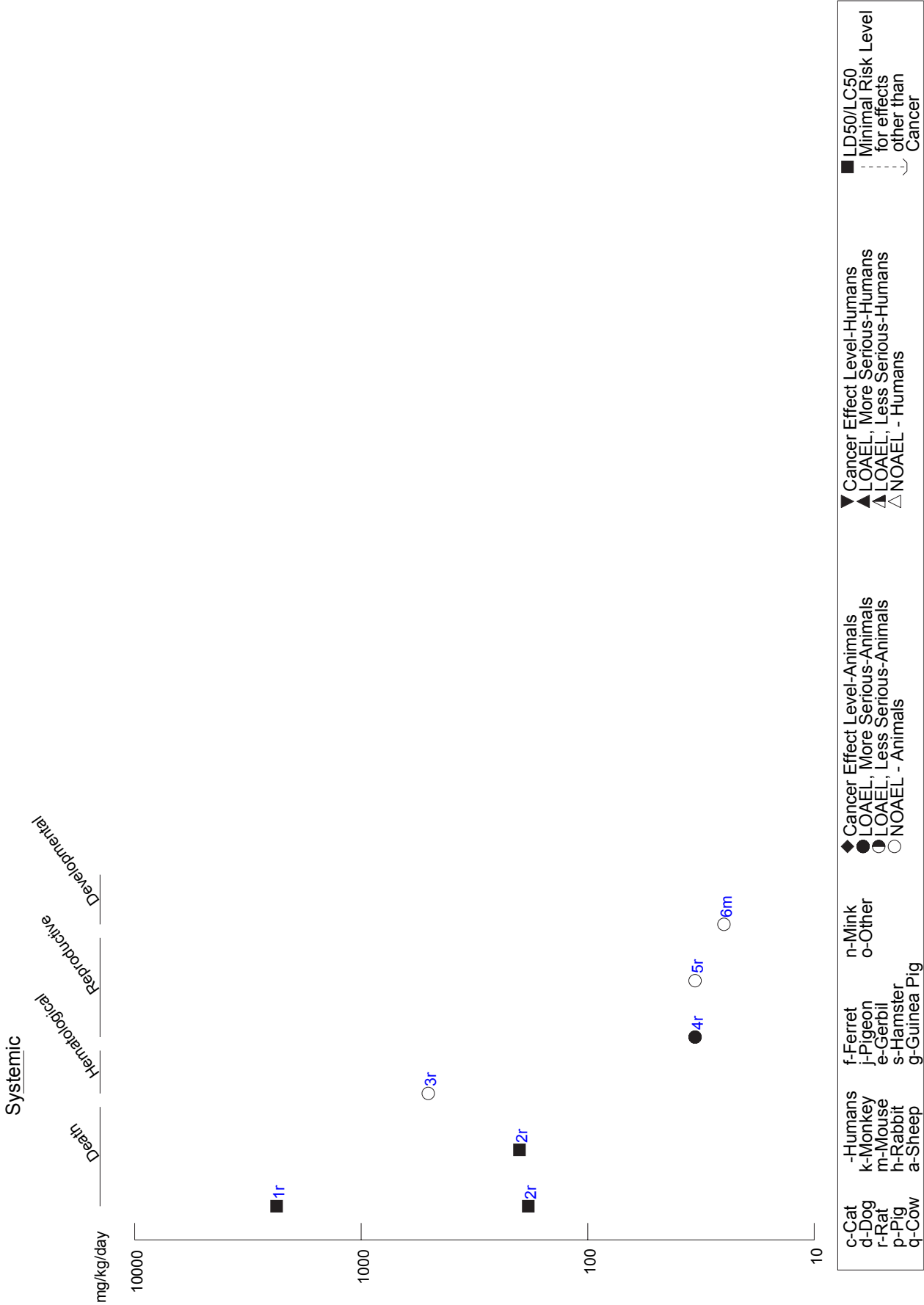


Figure 3-4 Levels of Significant Exposure to Chromium III - Oral (Continued)

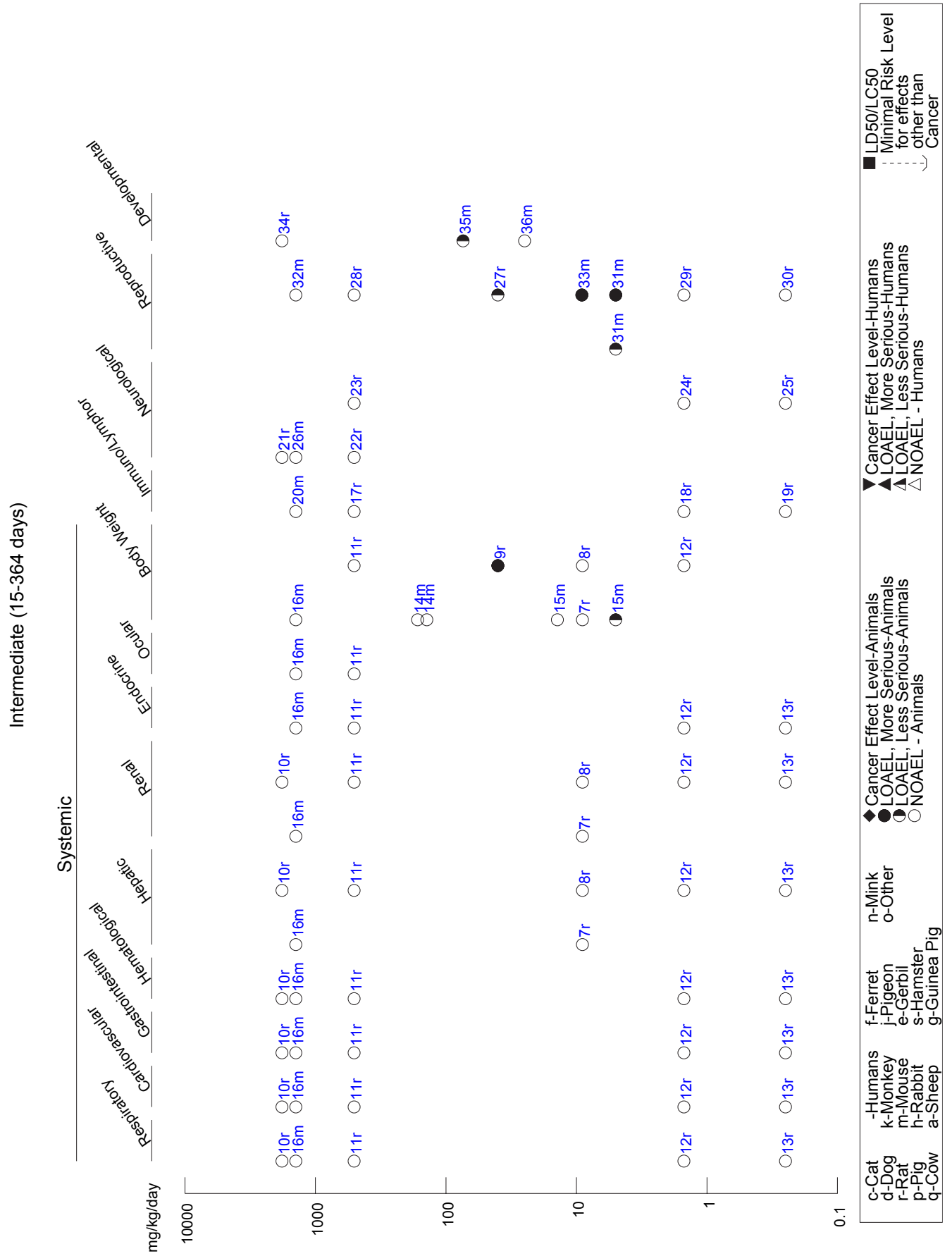
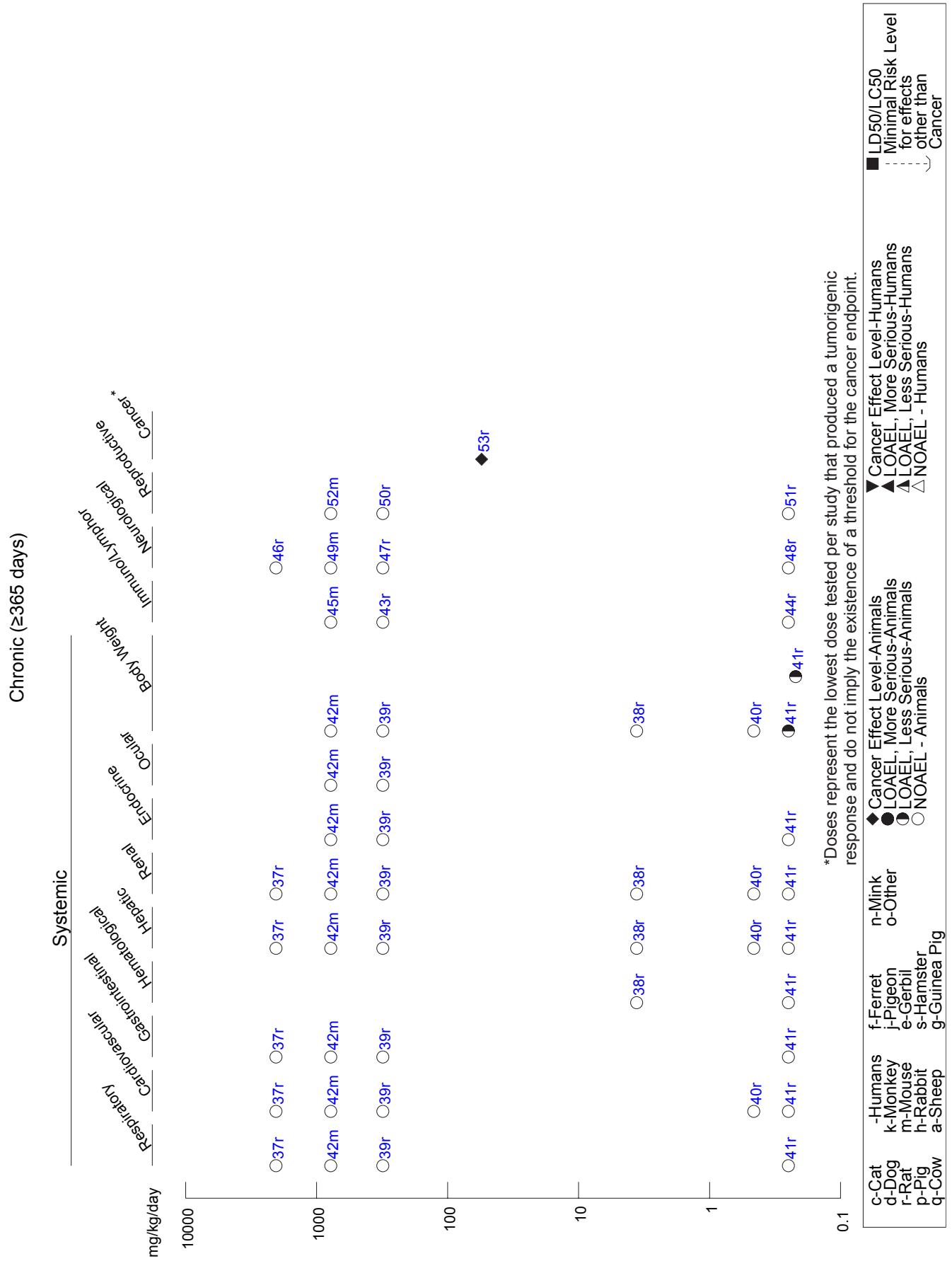


Figure 3-4 Levels of Significant Exposure to Chromium III - Oral (Continued)



3. HEALTH EFFECTS

nicotinate, chromium oxide and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975).

Cardiovascular Effects. Case reports of humans who died after ingesting chromium(VI) compounds have described cardiovascular effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed early hypoxic changes in the myocardium (Ellis et al. 1982). In another case, cardiac output, heart rate, and blood pressure dropped progressively during treatment in the hospital of a 17-year-old male who had ingested 29 mg chromium(VI)/kg as potassium dichromate. He died of cardiac arrest. Autopsy revealed hemorrhages in the anterior papillary muscle of the left ventricle (Clochesy 1984; Iserson et al. 1983). Cardiovascular effects have not been reported at nonlethal doses. No information was identified on cardiovascular effects in humans after oral exposure to chromium(III) compounds.

No studies were located regarding effects on cardiovascular function in animals after oral exposure to chromium(VI) compounds. Soudani et al. (2011c) found fibrosis, necrosis, vacuolization, and hemorrhage in the heart of rats dosed with 26 mg chromium(VI)/kg/day as potassium dichromate for 3 weeks. However, in other studies, histopathological examination of the heart of rats and mice exposed to oral chromium(VI) (as sodium dichromate dehydrate and sodium acetate) and chromium(III) (as chromium nicotinate, chromium oxide and chromium picolinate) for durations of 3 months to 2 years, revealed no abnormalities (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Schroeder et al. 1965; Shara et al. 2005, 2007). For chromium(VI) compounds (administered as sodium dichromate dihydrate in drinking water), the highest doses tested for intermediate-duration exposures were 20.9 mg chromium(VI)/kg/day in rats and 27.0 mg chromium(VI)/kg/day in mice; for chronic exposure durations the highest concentrations were 7.0 mg chromium(VI)/kg/day for rats and 8.7 chromium(VI)/kg/day for mice (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975). None of these studies assessed cardiovascular end points such as blood pressure or electrocardiograms.

Gastrointestinal Effects. Cases of gastrointestinal effects in humans after oral exposure to chromium(VI) compounds have been reported. In one study, a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate experienced abdominal pain and vomiting before death. Autopsy revealed gastrointestinal ulceration (Kaufman et al. 1970). In another study, a 44-year-old man died of gastrointestinal hemorrhage after ingesting 4.1 mg chromium(VI)/kg as chromic acid solution (Saryan and Reedy 1988). Gastrointestinal hemorrhage and extensive necrosis of all digestive mucous membranes were also observed on autopsy of a 35-year-old woman who died following ingestion of 357 mg chromium(VI)/kg as chromic acid (Loubieres et al. 1999). Gastrointestinal burns and hemorrhage have also been described as contributing to the cause of death of infants who ingested unknown amounts of sodium dichromate (Ellis et al. 1982) or ammonium dichromate (Reichelderfer 1968) and a 17-year-old male who ingested ~29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983).

Some chromium(VI) compounds, such as potassium dichromate and chromium trioxide, are caustic and irritating to mucosal tissue. A 25-year-old woman who drank a solution containing potassium dichromate experienced abdominal pain and vomited (Goldman and Karotkin 1935). Two people who ate oatmeal contaminated with potassium dichromate became suddenly ill with severe abdominal pain and vomiting, followed by diarrhea (Partington 1950). Acute gastritis developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965). Nausea, hematemesis, and bloody diarrhea were reported in a 24-year-old woman who ingested ammonium dichromate in a suicide attempt (Hasan 2007).

Ingestion of chromium compounds as a result of exposure at the workplace has occasionally produced gastrointestinal effects. In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, in addition to symptoms of labored breathing, dizziness, headache, and weakness from breathing the fumes during work, workers experienced nausea and vomiting upon eating on the premises (Lieberman 1941). Gastrointestinal effects were also reported in an epidemiology study of 97 workers in a chromate plant exposed to dust containing both chromium(III) and chromium(VI) compounds. Blocked nasal passages, as a result of working in the dust laden atmosphere, forced the individuals to breathe through their mouths, thereby probably ingesting some of the chromium dust. A 10.3% incidence of gastric ulcer formation and a 6.1% incidence of hypertrophic gastritis was reported. Epigastric and substernal pain were also reported in the chromate production workers (Mancuso 1951). Gastric mucosa irritation resulting in duodenal ulcer, possibly as a result of mouth breathing, has

also been reported in other studies of chromate production workers (Sassi 1956; Sterekhova et al. 1978). Subjective symptoms of stomach pain, duodenal ulcers, gastritis, stomach cramps, and indigestion were reported by workers exposed to a mean concentration of 0.004 mg chromium(VI)/m³ in an electroplating facility where zinc, cadmium, nickel, tin, and chromium plating were carried out (Lucas and Kramkowski 1975). An otolaryngological examination of 77 employees of eight chromium electroplating facilities in Czechoslovakia, where the mean level in the breathing zone above the plating baths was 0.414 mg chromium(VI)/m³, revealed 12 cases of chronic tonsillitis, 5 cases of chronic pharyngitis, and 32 cases of atrophic changes in the left larynx (Hanslian et al. 1967). These effects were probably also due to exposure via mouth breathing.

In a cross-sectional study conducted in 1965 of 155 villagers whose well water contained chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The highest concentration of chromium(VI) detected during sampling was 20 mg chromium(VI)/L, equivalent to a dose of 0.57 mg chromium(VI)/kg/day based on a default reference water consumption rate and body weight value of 2 L/day and 70 kg, respectively (note that these values may not be appropriate for the Chinese study population). However, exposure estimates for this population are uncertain and it is likely that exposure levels in many cases were to concentrations less than 20 mg chromium(VI)/L. At least some residents obtained drinking water from alternative sources (Sedman et al. 2006) and exposure may have been self-limiting due to lack of palatability of water (Beaumont et al. 2008). Thus, exposure levels associated with adverse effects are not well characterized.

No information was identified on gastrointestinal effects in humans after oral exposure to chromium(III) compounds.

Oral exposure of animals to chromium(VI), but not chromium(III), compounds results in irritation and histopathological changes to tissues of the gastrointestinal tract. Gastrointestinal hemorrhage was observed in rats given a lethal gavage dose of potassium dichromate (130 mg chromium(VI)/kg) (Samitz 1970). Histopathological changes were observed in rats and mice exposed to chromium(VI) as sodium dichromate dihydrate in drinking water for 8 days (Thompson et al. 2011, 2012), 3 months (NTP 2007; Thompson et al. 2011, 2012), or 2 years (NTP 2008a). After 8 days of exposure, villous atrophy and

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crypt cell hyperplasia were observed in the duodenum and jejunum of rats exposed to ≥ 10 mg chromium(VI)/kg/day (Thompson et al. 2012) and cytoplasmic vacuolization was observed in the duodenum in mice exposed to 30 mg chromium(VI)/kg/day (Thompson et al. 2011). Following exposure for 3 months, duodenal histiocytic infiltration of the duodenum was observed in male and female F344/N rats exposed at ≥ 2.9 mg chromium(VI)/kg/day (NTP 2007; Thompson et al. 2012); crypt cell hyperplasia, apoptosis, and histiocytic infiltration were observed in the duodenum and jejunum at 7.1 mg chromium(VI)/kg/day (Thompson et al. 2012). At the highest daily dose (20.9 mg chromium(VI)/kg/day), ulcer and epithelial hyperplasia and metaplasia of the glandular stomach were observed (NTP 2007). Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at ≥ 3.1 and ≥ 5.2 mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at ≥ 2.8 mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and ≥ 5.2 in the C57BL/6 strain, and histiocytic cellular infiltration at ≥ 2.8 mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and ≥ 5.2 mg chromium(VI)/kg/day in the BALB/c strain. After exposure for 2 years, duodenal histiocytic infiltration was observed in male and female rats exposed at 0.77 and 2.4 mg chromium(VI)/kg/day, respectively; in mice, duodenal epithelial hyperplasia was observed at 0.38 mg chromium(VI)/kg/day for 2 years and histiocytic cellular infiltration of the duodenum was also observed in males at 2.4 mg chromium(VI)/kg/day and females at 3.1 mg chromium(VI)/kg/day. In the 2-year study (NTP 2008a), neoplasms of the squamous epithelium of the oral mucosa and tongue were observed in rats and of the small intestine (duodenum, jejunum and ileum) were observed in mice; these findings are discussed in Section 3.2.2.7 (Oral Exposure, Cancer). In female mice exposed to 0.38 mg chromium(VI)/kg/day and male mice exposed to 2.4 mg chromium(VI)/kg/day for 2 years, cytoplasmic alteration of the pancreas (depletion of cytoplasm zymogen granules) was observed; NTP stated that the biological significance of this finding was uncertain (NTP 2008a). In contrast to the findings in the NTP, 3-month and 2-year drinking water studies of sodium dichromate dihydrate (NTP 2007, 2008a), no histopathological changes to the gastrointestinal tract were observed in BALB/c mice exposed to dietary potassium dichromate at doses up to 36.7 mg chromium(VI)/kg/day in a multigeneration continuous breeding study (NTP 1997). Differences in results of these studies could be attributed to difference in the exposure media (water versus feed). Data from the 2-year drinking water study on sodium dichromate dihydrate in mice (NTP 2008a) were used to develop the chronic-duration oral MRL for chromium(VI) compounds. The BMDL₁₀ value of 0.09 mg chromium(VI)/kg/day for diffuse epithelial hyperplasia of the duodenum in female mice was used to calculate an oral MRL of 0.0009 mg chromium(VI)/kg/day for chronic-duration exposure to chromium(VI) compounds as described in the footnote of Table 3-4.

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No histopathological changes to the stomach or small intestine were observed in mice and rats exposed to oral chromium(III) (as chromium nicotinate, chromium oxide, and chromium picolinate) for 3 months or 2 years (Ivankovic and Preussmann 1975; NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). The highest doses of chromium(III) tested were 1,415 mg chromium(III)/kg/day as chromium picolinate in the diet for 3 months (NTP 2008b; Rhodes et al. 2005) and 2,040 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975).

Hematological Effects. Cases of hematological effects have been reported in humans after the ingestion of lethal or sublethal doses of chromium(VI) compounds. In a case of an 18-year-old woman who ingested a few grams of potassium dichromate, decreased hemoglobin content and hematocrit, and increased total white blood cell counts, reticulocyte counts, and plasma hemoglobin were found 4 days after ingestion. These effects were indicative of intravascular hemolysis (Sharma et al. 1978). A 25-year-old woman who drank a solution containing potassium dichromate had a clinically significant increase in leukocytes due to a rise in polymorphonuclear cells (Goldman and Karotkin 1935). In another study, a 44-year-old man had decreased hemoglobin levels 9 days after ingestion of 4.1 mg chromium(VI)/kg as chromic acid solution that probably resulted from gastrointestinal hemorrhage (Saryan and Reedy 1988). Inhibition of blood coagulation was described in a case of a 17-year-old male who died after ingesting ~29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). Anemia following severe hemorrhaging developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis, which saved his life (Fristedt et al. 1965).

In a cross-sectional study conducted in 1965 of 155 villagers whose well water contained 20 mg chromium(VI)/L as a result of pollution from an alloy plant in the People's Republic of China, associations were found between drinking the contaminated water and leukocytosis and immature neutrophils. The alloy plant began chromium smelting in 1961 and began regular production in 1965. Similar results were found in two similar studies in other villages, but further details were not provided (Zhang and Li 1987). The highest concentration of chromium(VI) detected during sampling was 20 mg chromium(VI)/L, equivalent to a dose of 0.57 mg chromium(VI)/kg/day. However, exposure estimates for this population are uncertain and it is likely that exposure levels in many cases were to concentrations <20 mg chromium(VI)/L. At least some residents obtained drinking water from alternative sources (Sedman et al. 2006) and exposure may have been self-limiting due to lack of palatability of water at

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higher concentrations (Beaumont et al. 2008). Thus, exposure levels associated with adverse effects are not well characterized.

No reliable information was identified on hematological effects in humans of oral exposure to chromium(III) compounds.

Microcytic, hypochromic anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb), was observed in F344/N rats and B6C3F1 mice exposed to chromium(III) compounds in drinking water for exposure durations ranging from 4 days to 1 year (NTP 2007, 2008a). Severity was dose-dependent. Maximum effects were observed after approximately 3 weeks of exposure; with increasing exposure durations (e.g., 14 weeks to 1 year), effects were less pronounced, presumably due to compensatory hematopoietic responses. In general, effects were more severe in rats than mice. Following acute exposure of male rats to sodium dichromate dihydrate in drinking water for 4 days, a slight, but statistically significant decrease (2.1%) in MCH was observed at 2.7 mg chromium(VI)/kg/day, but not at 0.7 mg chromium(VI)/kg/day. With increasing doses (7.4 mg chromium(VI)/kg/day and greater), additional decreases in MCH and decreased MCV were observed (NTP 2008a). Similar effects were observed in male and female rats exposed for 5 days, with effects observed at 4.0 and 4.1 chromium(VI)/kg/day, respectively (NTP 2007); a NOAEL was not established.

More severe microcytic, hypochromic anemia occurred in rats and mice following exposure to sodium dichromate dihydrate in drinking water for 22 or 23 days (NTP 2007, 2008a). Decreased Hct (6.1%), Hgb (8.4%), MCV (7.7%), and MCH (10.6%) occurred in male rats exposed for 22 days to 0.77 mg chromium(VI)/kg/day, with decreases exhibiting dose-dependence; effects were not observed at 0.21 mg chromium(VI)/kg/day (NTP 2008a). Similar hematological effects were observed in male and female rats exposed to 1.7 mg chromium(VI)/kg/day for 23 days (NTP 2007). In female mice exposed to 22 days, slight, but significant decreases in MCV (2.0%) and MCH (1.2%) were observed at 0.38 mg chromium(VI)/kg/day, with more severe effects at higher doses (NTP 2008a). After exposure for 3 months to 1 year, microcytic, hypochromic anemia in rats and mice was less severe than that observed after 22 or 23 days (NTP 2007, 2008a). For example in male rats exposed for 22 days, decreases in Hct (6.1%), Hgb (8.4%), MCV (7.7%), and MCH (10.6%) were observed at 0.77 mg chromium(VI)/kg/day, whereas after exposure to 0.77 mg chromium(VI)/kg/day for 1 year, decreased MCH (2.4%), but not MCV, Hct, or Hgb, were observed (NTP 2008a). Similar decreases in severity was also observed in female rats and in male and female mice exposed for 1 year compared to 22 days (NTP 2008a). In

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contrast, routine hematological examination revealed no changes in Sprague-Dawley rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958); however, data on hematological parameters or statistical analyses were not presented in the report. A 91-day study found decreases in serum iron levels and bone marrow iron content in rats exposed to 7.1 or 21 mg chromium(VI)/kg/day as sodium dichromate dehydrate in drinking water (Thompson et al. 2012); however, no alterations in blood ferritin or transferrin levels were found. No alterations in iron status were observed in mice similarly exposed to 31 mg chromium(VI)/kg/day (Thompson et al. 2011). Data from the 22-day evaluation in the 2-year NTP (2008a) drinking water study on sodium dichromate dihydrate in rats were used to develop the intermediate-duration oral MRL for chromium(VI) compounds. Because several hematological parameters are used to define the clinical picture of anemia, the intermediate-duration oral MRL was based on the average BMDL_{2sd} value (e.g., the average of BMDL_{2sd} values for Hgb, MCV, and MCH; BMD models did not provide adequate fit for hematocrit) of 0.52 mg chromium(VI)/kg/day, as described in the footnote of [Table 3-4](#).

In feeding studies of potassium dichromate in Sprague-Dawley rats and BALB/c mice, slight microcytic hypochromic anemia, characterized by slightly reduced MCV and MCH values was observed (NTP 1996a, 1996b, 1997). In rats and mice fed potassium dichromate for 9 weeks, MCV and MCH values, were decreased at the highest concentration only, which was equivalent to 8.4 and 9.8 mg chromium(VI)/kg/day in male and female rats, respectively (NTP 1996b), and 32.2 and 48 mg chromium(VI)/kg/day in male and female mice, respectively (NTP 1996a). These effects did not occur at lower dietary concentrations equivalent to ≤ 2.1 or ≤ 2.45 mg chromium(VI)/kg/day for male and female rats, respectively, or to ≤ 7.35 or ≤ 12 mg chromium(VI)/day for male and female mice, respectively. In a multigeneration study of mice given potassium dichromate in the diet, F₁ males had decreased MCVs at dietary concentrations equivalent to 16 and 36.7 mg chromium(VI)/kg/day and decreased MCH values at 36.7 mg chromium(VI)/kg/day (NTP 1997). F₁ females had dose-related decreased MCV at concentrations equivalent to ≥ 7.8 mg chromium(VI)/kg/day. Since 7.8 mg chromium(VI)/kg/day was the lowest dose in the study, a no effect level was not identified. Compared to results of the drinking water studies on sodium dichromate dihydrate (NTP 2007, 2008a), hematological effects observed in the dietary studies on potassium dichromate (NTP 1996a, 1996b, 1997) occurred at higher daily doses. Differences may be related to differences in the exposure media (feed versus drinking water).

No hematological effects were observed in animals after oral exposure to chromium(III) compounds for exposure durations ranging from acute to chronic. Exposure of F344/N rats to chromium picolinate in the diet for 3 days at doses up to 506 mg chromium(III)/kg/day did not produce hematological effects (NTP

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2008b). For intermediate duration exposure, no hematological effects were observed in rats exposed to chromic oxide in the diet at doses up to 1,806 chromium(III)/kg/day for 3 months (Ivankovic and Preussmann 1975), in rats and mice exposed to chromium picolinate in the diet at 506 and 1,415 mg chromium(III)/kg/day, respectively, for 3 months (NTP 2008b), or in rats chromium nicotinate in the diet at 1.5 or 0.25 mg chromium(III)/kg/day for 3 months or 38 weeks, respectively (Shara et al. 2005). For chronic exposure durations, no hematological abnormalities were found in rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), or in rats exposed to 0.25 mg chromium(III)/kg/day as chromium nicotinate for 2 years (Shara et al. 2007).

Musculoskeletal Effects. No information regarding musculoskeletal effects in humans exposed to oral chromium(VI) compounds was identified. The development of rhabdomyolysis was reported in a 24-year-old woman who ingested dietary supplements containing chromium(III) picolinate (Martin and Fuller 1998). Over a 48-hour period, the patient ingested 1,200 µg of chromium(III) picolinate, equivalent to 148.8 µg of chromium(III) or 2.2 µg of chromium(III)/kg body weight (based on a reported body weight of 67 kg) over a 48-hour period. Upon evaluation 4 days after initially ingesting the dietary supplement, she reported muscle pain on palpation and had muscular hypertrophy and elevated serum creatine kinase, although no myoglobin was detected in urine. In addition to chromium(III) picolinate, the dietary supplements contained numerous other substances.

Increases in serum creatine kinase (CK) activity were observed in F344/N rats following acute and intermediate exposure to sodium dichromate dihydrate in drinking water (NTP 2007). After exposure for 5 days, serum CK activity was increased in males by 31% at 31.8 mg chromium(VI)/kg/day and in females by 46% at 16.4 mg chromium(VI)/kg/day; after exposure for 13 weeks, serum CK activity was increased by 70% and 50% in males and females, respectively, at 5.9 mg chromium(VI)/kg/day. Since serum CK activity increased with dose, NTP (2007) suggested that findings were consistent with muscle injury. After exposure of rats for 12 months to 2.4 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water, serum CK activity was increased by 64% (NTP 2008a). No information regarding musculoskeletal effects in animals exposed to oral chromium(III) compounds was identified.

Hepatic Effects. Effects on the liver have been described in case reports of humans who had ingested chromium(VI) compounds. Liver damage, evidenced by the development of jaundice, increased bilirubin, and increased serum lactic dehydrogenase, was described in a case of a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium

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trioxide/L (Fristedt et al. 1965). In another adult, increased alanine and aspartate aminotransferase, γ -glutamyl transferase, and bilirubin levels were observed 4 days after accidental ingestion of 20% chromic acid (Barešić et al. 2009). In a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate, high levels of the liver enzymes, aspartate aminotransferase and alanine aminotransferase, were found in the serum 24 hours after ingestion. Upon postmortem examination, the liver had marked necrosis (Kaufman et al. 1970). Fatty degeneration of the liver was observed on autopsy of a 35-year-old female who died after ingesting approximately 257 mg chromium(VI)/kg (assuming a 70-kg body weight) as chromic acid in a suicide (Loubieres et al. 1999).

Effects on the liver of rats and mice exposed to oral chromium(VI) compounds for acute, intermediate and chronic durations have been detected by biochemical and histochemical techniques. In male and female F344/N rats exposed to 4.0 and 4.1 mg chromium(VI)/kg/day, respectively, as disodium dichromate in drinking water for 5 days, serum alanine aminotransferase (ALT) activity was increased by 15 and 30%, respectively (NTP 2007). After 14 weeks of exposure, serum ALT activity was increased by 14% in male rats and by 30% in female rats and serum sorbitol dehydrogenase (SDH) activity was increased by 77% in male rats and 359% in female rats at 1.7 mg chromium(VI)/kg/day (NTP 2007). In females, morphological changes to the liver included cellular histiocyte infiltration and chronic focal inflammation at doses of 3.5 and 20.9 mg chromium(VI)/kg/day, respectively; no morphological changes were observed in male rats, indicating that female rats may be more sensitive than males. However, similar exposure to B6C3F1 mice to 27.9 mg chromium(VI)/kg/day for 14 weeks produced no effects on serum liver enzymes or hepatic morphology (NTP 2007). Increased serum ALT and aspartate aminotransferase (AST) activities and hepatic morphological changes (vacuolization, increased sinusoidal space, and necrosis) were observed in rats exposed to 1.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 22 weeks (Acharya et al. 2001). Increased serum ALT (253%) and histopathological changes (focal necrosis and degeneration with changes in vascularization) were reported in Wistar rats exposed to chromium(VI) (compound not specified) in drinking water for 10 weeks (Rafael et al. 2007). Rats treated by gavage with 13.5 mg chromium(VI)/kg/day as potassium chromate for 20 days had increased accumulations of lipids (Kumar and Rana 1982) and changes and relocation of liver enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, cholinesterase, and lipase) (Kumar et al. 1985), as determined by histochemical means. In another study, no treatment-related histological changes in liver cells were observed in groups of Sprague-Dawley rats containing 24 males and 48 females that were exposed to chromium(VI) as potassium dichromate in the diet for 9 weeks followed by a recovery period of 8 weeks (NTP 1996b). Average daily ingestion of chromium(VI) for males was 1, 3, 6, and 24 mg/kg/day and 1, 3, 7, and 28 mg/kg/day for females. Although no indication

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of hepatic effects was found in mice exposed to ≤ 36.7 mg/kg/day in a multigeneration feeding study (NTP 1997), some indication of liver toxicity was found in a 9-week feeding study in BALB/c mice exposed to 1.1, 3.5, 7.4, and 32 mg chromium(VI)/kg/day for males and 1.8, 5.6, 12, and 48 mg chromium(VI)/kg/day for females (NTP 1996a). Hepatocyte cytoplasmic vacuolization occurred in 1/6 males at 3.5 mg/kg/day, 2/5 males at 7.4 mg/kg/day, and 2/6 males at 32 mg/kg/day, and in 1/12 control females, 0/12 females at 1.8 mg/kg/day, 3/12 females at 5.6 mg/kg/day, 2/12 females at 12 mg/kg/day, and 4/12 females at 48 mg/kg/day. The vacuoles were small, clear, and well demarcated, which is suggestive of lipid accumulation. The small number of animals and lack of a clear dose-response preclude a definitive conclusion as to whether this effect was toxicologically significant. For chronic exposure durations, adverse liver effects have been observed in F344/N rats and B6C3F1 mice exposed to chromium(VI) as sodium chromate dihydrate in drinking water (NTP 2008a). In male rats exposed for 1 year to 0.77 mg chromium(VI)/kg/day, serum ALT activity was increased by 156%. After exposure for 2 years, histopathological examination of the liver showed the following morphological changes, with females of both species appearing more sensitive than males: chronic inflammation (2.1 mg chromium(VI)/kg/day), histiocytic cellular infiltration (5.9 mg chromium(VI)/kg/day) and basophilic foci (0.77 mg chromium(VI)/kg/day) in male rats; chronic inflammation (0.24 mg chromium(VI)/kg/day), histiocytic cellular infiltration (0.94 mg chromium(VI)/kg/day) and fatty change (0.94 mg chromium(VI)/kg/day) in female rats; clear cell and eosinophilic foci in male mice (5.9 mg chromium(VI)/kg/day); and histiocytic cellular infiltration (0.38 mg chromium(VI)/kg/day) and chronic inflammation (3.1 mg chromium(VI)/kg/day) in female mice (NTP 2008a). No morphological changes, however, were detected in the livers of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year (MacKenzie et al. 1958).

No evidence of liver damage has been observed in rats and mice treated with oral chromium(III) compounds for intermediate and chronic exposure durations, based on histopathological examination of the liver. For intermediate-duration exposures, no morphological changes were observed in rats exposed to 1,806 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 90 days (Ivankovic and Preussmann 1975), rats exposed to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate in the diet for 20 weeks (Anderson et al. 1997b), rats exposed to 506 mg chromium(III)/kg/day and mice exposed to 1,415 mg chromium(III)/kg/day as chromium picolinate in the diet for 14 weeks (NTP 2008b; Rhodes et al. 2005), or rats exposed to chromium nicotinate in the diet at 1.5 mg chromium(III)/kg/day for 14 weeks or 0.25 mg chromium(III)/kg/day as chromium nicotinate for 38 weeks (Shara et al. 2005, 2007). For chronic-duration exposures, histological examination revealed no morphological changes in the livers of rats exposed to chromium oxide in the diet 5 days/week at

2,040 mg chromium(III)/kg/day for 2 years (Ivankovic and Preussmann 1975), rats exposed to 3.6 mg chromium(III)/kg/day as chromium trichloride in the drinking water for 1 year (MacKenzie et al. 1958), of rats exposed to 513 mg chromium(III)/kg/day and mice exposed to 781 mg chromium(III)/kg/day as chromium picolinate in the diet for 2 years (NTP 2008b), rats exposed to 0.25 mg chromium(III)/kg/day as chromium nicotinate in the diet for 2 years (Shara et al. 2005, 2007), or rats exposed to 0.46 mg chromium(III)/kg/day as chromium acetate in the drinking water for 2–3 years (Schroeder et al. 1965).

Renal Effects. Case studies were located regarding renal effects in humans after oral exposure to chromium(VI) compounds. Acute renal failure, characterized by proteinuria, and hematuria, and followed by anuria, developed in a chrome plating worker who had accidentally swallowed an unreported volume of a plating fluid containing 300 g chromium trioxide/L. He was treated by hemodialysis (Fristedt et al. 1965). Necrosis of renal tubules was found upon autopsy of a 22-month-old boy who died after ingesting an unknown amount of sodium dichromate (Ellis et al. 1982) and of a 17-year-old boy who died after ingesting 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983). A fatal ingestion of 4.1 mg chromium(VI)/kg as a chromic acid solution in a 44-year-old man resulted in acute tubular necrosis and renal failure (Saryan and Reedy 1988). In an adult consuming a nonlethal dose of 20% chromic acid, a rapid decrease in urine output progressing to anuria was observed within 4 days of ingestion; abdominal ultrasound revealed enlarged kidneys with edematous cortex and pronounced pyramids without other pathology (Barešić et al. 2009). A 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate died from renal failure 8 days after he was admitted to the hospital. Upon postmortem examination, the kidneys were pale, enlarged, and necrotic with tubular necrosis and edema (Kaufman et al. 1970). Acute renal failure and necrosis also observed on autopsy of a 35-year-old woman who died following ingestion of 357 mg chromium(VI)/kg as chromic acid (Loubieres et al. 1999). Another case study of an 18-year-old woman who ingested a few grams of potassium dichromate reported proteinuria, oliguria, and destruction of the tubular epithelium of the kidneys. She regained renal function following dialysis (Sharma et al. 1978). Proteinuria and oliguria were also observed after ingestion of potassium dichromate by a 25-year-old woman (Goldman and Karotkin 1935).

Acute renal failure was reported in a 24-year-old man who ingested an unknown quantity of a dietary supplement (Arsenal X[®]) containing chromium picolinate daily for 2 weeks (Wani et al. 2006). Serum creatinine was elevated approximately 3 times above the normal range, blood urea nitrogen was elevated slightly above normal range, urinalysis was positive for protein, and renal biopsy showed acute tubular necrosis. The patient developed severe impairment of renal function that required hemodialysis. Renal

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function improved within 4 weeks of discontinuation of treatment with the supplement. Chemical analysis of the dietary supplement was not conducted and the patient's plasma chromium levels were not obtained. Adverse renal effects were reported in a 49-year-old woman who ingested 600 µg of chromium(III) picolinate (equivalent to 74.4 µg chromium(III)/day or 1.1 µg chromium(III)/kg/day, assuming a body weight of 70 kg) daily for 6 weeks (Wasser et al. 1997). The patient was evaluated approximately 5 months after initiating the 6-week treatment. Serum creatinine levels were approximately 6 times above the normal range, blood urea nitrogen was approximately 4 times above the normal range, and trace amounts of blood were found in the urine. Renal biopsy showed severe chronic active interstitial nephritis. After 2 months of treatment with prednisone, serum creatinine levels were approximately 4 times above the normal range (other values were not reported). Chemical analysis of the dietary supplement was not conducted and the patient's plasma chromium levels were not obtained.

Renal effects have been observed in animals following oral exposure to chromium(VI), but not chromium(III), compounds. Effects on the kidneys of rats exposed to potassium chromate have been detected by biochemical and histochemical techniques. Rats treated by gavage with 13.5 mg chromium(VI)/kg/day for 20 days had increased accumulation of lipids and accumulated triglycerides and phospholipids in different regions of the kidney than controls (Kumar and Rana 1982). Similar treatment of rats also resulted in inhibition of membrane and lysosomal enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, and lipase) in the kidneys (Kumar and Rana 1984). Histopathological changes to the kidneys, including vacuolization in glomeruli, degeneration of basement membrane of Bowman's capsule, and renal tubular epithelial degeneration, were observed in Wistar rats exposed to 1.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 22 weeks (Acharya et al. 2001). Oliguria and proteinuria were observed in Wistar rats exposed to 100 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). Significant reductions in creatinine clearance and renal hemorrhage, necrosis, and enlarged glomeruli space were observed in rats exposed to 9.4 mg chromium(VI)/kg/day as potassium dichromate in drinking water during pregnancy and lactation (Soudani et al. 2010b) or 3.4 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 21 days (Soudani et al. 2010a). However, histological examination revealed no morphological changes in the kidneys of rats exposed to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water for 1 year (MacKenzie et al. 1958). Results of studies in rats and mice conducted by NTP (1996a, 1996b, 1997, 2007, 2008a) also show no histopathological changes in kidneys following intermediate-or chronic-duration exposure to chromium(VI) compounds in the diet or drinking water. The respective highest doses of chromium(VI) tested for intermediate and chronic exposure durations were 48 mg chromium(VI)/kg/day in mice

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exposed to dietary potassium dichromate for 9 weeks (NTP 1996a) and 8.7 chromium(VI)/kg/day, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a).

Exposure of mice and rats to chromium(III) compounds (chromium acetate, chromium nicotinate, chromium oxide, chromium picolinate, and chromium trichloride) in food or drinking water for up to 2 years did not result in renal damage, based on histopathological examination of kidneys (Anderson et al. 1997b; Ivankovic and Preussmann 1975; MacKenzie et al. 1958; NTP 2008b; Schroeder et al. 1965; Shara et al. 2005, 2007). The respective highest doses of chromium(III) tested for intermediate and chronic exposure durations were 1,806 mg chromium(III)/kg/day as chromium oxide in the diet 5 days/week for 3 months and 2,040 mg chromium(III)/kg/day chromium oxide in the diet 5 days/week for 2 years (Ivankovic and Preussmann 1975). Renal function was not assessed in these studies.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to chromium(VI) or (III) compounds. Serum prolactin levels were decreased by 59% in male Wistar rats exposed to 74 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days (Quinteros et al. 2007). Histopathological examination of the endocrine tissues (including adrenal gland, parathyroid, and thyroid) has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,415 and 781 mg chromium(III)/kg/day, respectively, as chromium picolinate in the diet for 3 months and 2 years, respectively (NTP 2008b; Rhodes et al. 2005). Endocrine function was not assessed in these studies.

Dermal Effects. Administration of 0.04 mg chromium(VI)/kg as potassium dichromate in an oral tolerance test exacerbated the dermatitis of a building worker who had a 20-year history of chromium contact dermatitis. A double dose led to dyshidrotic lesions (vesicular eruptions) on the hands (Goitre et al. 1982). Dermatitis in 11 of 31 chromium-sensitive individuals worsened after ingestion of 0.036 mg chromium(VI)/kg as potassium dichromate (Kaaber and Veien 1977). The sensitizing exposures were not discussed or quantified. No information regarding dermal effects of oral exposure of humans to chromium(III) compounds was identified.

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No studies were located regarding noncancer dermal effects in animals after oral exposure to chromium(VI) or chromium(III) compounds. The effect of oral exposure to chromium(VI) compounds on increased susceptibility of hairless mice to ultraviolet light-induced skin cancer is discussed in Section 3.2.2.7 (Oral Exposure, Cancer).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to chromium(VI) or chromium(III) compounds. Histopathologic examination of rats and mice exposed to sodium dichromate dihydrate in drinking water at 20.9 and 27.9 mg chromium(IV)/kg/day, respectively, for 3 months or at 7.0 and 8.7 mg chromium(IV)/kg/day, respectively, for 2 years revealed normal morphology of the ocular tissue (NTP 2007, 2008a). Similar negative findings were observed in rats and mice exposed to chromium(III) as dietary chromium picolinate at 506 and 1415 mg chromium(III)/kg/day, respectively, for 3 months or at 313 and 781 mg chromium(III)/kg/day, respectively, for 2 years (NTP 2008b).

Body Weight Effects. Studies reporting body weight effects in humans exposed to chromium(VI) were not identified. The potential beneficial effect of dietary supplementation with chromium(III) (as chromium picolinate or other chromium(III) compounds) to aid in weight loss and increase lean body mass has been reported. Although the role of chromium(III) in the regulation of lean body mass, percentage body fat, and weight reduction is highly controversial with negative and positive results being reported in the literature, studies assessing these effects were not designed to evaluate weight loss as a toxicological end point (Anderson 1998b). Thus, body weight effects associated with dietary supplementation with chromium(III) compounds is not considered adverse (see Section 2.2 for additional information).

Significant decreases in body weight have been reported in several intermediate-duration oral chromium(VI) studies in animals (Bataineh et al. 1997; Chowdhury and Mitra 1995; De Flora et al. 2006; Elbetieha and Al-Hamood 1997; NTP 1996a, 1996b, 2007; Quinteros et al. 2007; Yousef et al. 2006). However, it should be noted that high concentrations of chromium in drinking water decrease palatability of water, resulting in decreased water consumption; thus, decreased body weight may, in part, be due to decreased water consumption, in addition to other causes. In male rats exposed to 73 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days, body weight was decreased by 11.6% (Quinteros et al. 2007). A 19% decrease in body weight gain was observed in male rats exposed to 42 mg chromium(VI)/kg/day (Bataineh et al. 1997) and a 10% decrease was reported in male mice exposed to 6 mg chromium(VI)/kg/day (Elbetieha and Al-Hamood 1997) as potassium dichromate

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in drinking water for 12 weeks. Note that daily doses in the study by Elbetieha and Al-Hamood (1997) may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). Final body weight was decreased in rats and mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks (NTP 2007). In rats, body weight was decreased in males by 11% at 11.2 mg chromium(VI)/kg/day and in females by 6% at 20.9 mg chromium(VI)/kg/day; in mice, body weight was decreased by 6% in males at 3.1 mg chromium(VI)/kg/day and by 8% in females at 5.2 mg chromium(VI)/kg/day. Decreases in body weight were also observed in male mice (9.3%) and female (13.5%) mice exposed to 165 and 14 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water for 210 days (De Flora et al. 2006). Gavage administration of 40 or 60 mg chromium(VI)/kg/day as sodium dichromate for 90 days resulted in 57 and 59% decreases in body weight gain, respectively (Chowdhury and Mitra 1995). In contrast, no changes in body weight gain were seen in rats or mice exposed to 9.8 or 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate in the diet for 9 weeks (NTP 1996a, 1996b) or in rabbits administered 3.6 mg chromium(VI)/kg/day by gavage as potassium dichromate (Yousef et al. 2006). No alterations in body weight gain were observed in rats chronically exposed (1 year) to 3.6 mg chromium(VI)/kg/day as potassium chromate in drinking water (Mackenzie et al. 1958). In contrast, final body weight was decreased by 12% in male rats at 5.9 mg chromium(VI)/kg/day and by 11% in female rats at 7.0 mg chromium(VI)/kg/day as sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a).

Several studies have examined the effect of exposure to potassium dichromate in drinking water on maternal body weight gain. An acute exposure (9 days) resulted in 8 and 24% decreases in body weight gain in pregnant mice exposed to 101 or 152 mg chromium(VI)/kg/day, respectively (Junaid et al. 1996b). Similarly, a decrease in maternal body weight gain was observed in pregnant mice exposed to 98 mg chromium(VI)/kg/day as potassium dichromate for 19 days (Trivedi et al. 1989). Reduced maternal body weight gains of 8, 14, and 21% were observed in rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Similar decreases in body weight gain (18 and 24%) were observed in rats exposed to 89 or 124 mg chromium(VI)/kg/day, respectively, for 3 months prior to mating (Kanojia et al. 1998). However, no alterations in maternal body weight gain were observed in a continuous breeding study in which rats were exposed to 36.7 mg chromium(VI)/kg/day as potassium dichromate in the diet (NTP 1997).

Conflicting results have been reported for alterations in body weight in rats and mice exposed to oral chromium(III) compounds for intermediate and chronic exposure durations. Dietary exposure to 9 mg chromium(III)/kg/day as chromium chloride or chromium picolinate for 20 weeks (Anderson et al. 1997b)

or 3.6 mg chromium(III)/kg/day as chromium chloride (Mackenzie et al. 1958) did not result in significant alterations in body weight gain. No alterations on body weight were observed in rats or mice exposed to dietary chromium picolinate for 14 weeks at doses up to 506 and 1,415 mg chromium(III)/kg/day, respectively (NTP 2008b; Rhodes et al. 2005) or in male and female mice exposed to chromic potassium sulfate in drinking water for 210 days at doses of 165 and 140 mg chromium(III)/kg/day, respectively (De Flora et al. 2006). No change in body weight was observed in male and female rats exposed to dietary chromium nicotinate for 90 days at 1.5 and 1.2 mg chromium(III)/kg/day, respectively (Shara et al. 2005); however, body weight was decreased by 8.1% in males at 0.22 mg chromium(III)/kg/day and by 11.4% in females at 0.25 mg chromium(III)/kg/day following exposure to dietary chromium nicotinate for 38 weeks (Shara et al. 2007). Exposure to chromium chloride in drinking water resulted in 14 and 24% decreases in body weight gain in rats exposed to 40 mg chromium(III)/kg/day for 12 weeks (Bataineh et al. 1997) and male mice exposed to 5 mg chromium(III)/kg/day for 12 weeks (Elbetieha and Al-Hamood 1997), respectively. Note that daily doses in the study by Elbetieha and Al-Hamood (1997) may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). No alterations in body weight gain were observed in rats or mice exposed to 0.46 or 0.48 mg chromium(III)/kg/day, respectively, as chromium acetate for a lifetime (Schroeder et al. 1964, 1965), or in mice and rats exposed to dietary chromium picolinate for 2 years at doses up to 313 and 781 mg chromium(III)/kg/day, respectively (NTP 2008b). However, exposure to dietary chromium nicotinate for 2 years resulted in a 14.9% decrease in male rats at 0.22 mg chromium(III)/kg/day and a 9.6% decrease in female rats at 0.25 mg chromium(III)/kg/day (Shara et al. 2007).

Metabolic Effects. Metabolic acidosis was observed in a 35-year-old female who died after ingesting approximately 257 mg chromium(VI)/kg (assuming a 70-kg body weight) as chromic acid in a suicide (Loubieres et al. 1999). No information on adverse metabolic effects of chromium(III) compounds in humans was identified. Serum glucose was elevated by 65% in male Wistar rats exposed to 3.7 mg chromium(VI)/kg/day (compound not specified) in drinking water for 10 weeks (Rafael et al. 2007). No changes in serum glucose were reported in rats and mice exposed to sodium dichromate dihydrate in drinking water for 3 months at doses up to 27.9 mg chromium(VI)/kg/day or for 2 years at doses up to 8.7 mg chromium(VI)/kg/day (NTP 2007, 2008a); however, data on serum glucose were not presented in the study reports. No information on adverse metabolic effects of chromium(III) compounds in animals was identified.

3.2.2.3 Immunological and Lymphoreticular Effects

The only reported effect of orally exposed humans on the immune system was the exacerbation of chromium dermatitis in chromium-sensitive individuals, as noted for dermal effects in Section 3.2.2.2. Sensitization of workers, resulting in respiratory and dermal effects, has been reported in numerous occupational exposure studies. Although the route of exposure for initial sensitization in an occupational setting is most likely a combination of inhalation, oral, and dermal routes, information on the exposure levels producing sensitization by the oral route was not identified. Additional information on contact dermatitis in sensitized workers is provided in Section 3.2.3.3 (Dermal Exposure, Immunological and Lymphoreticular Effects).

Oral exposure of animals to chromium(VI), but not chromium(III), compounds resulted in functional and histopathological changes to the immune system (NTP 2007, 2008a; Snyder and Valle 1991). Splenocytes prepared from rats given potassium chromate in drinking water at 16 mg chromium(VI)/kg/day for 3 weeks showed an elevated proliferative response of T- and B-lymphocytes to the mitogens, concanavalin A and liposaccharide, compared with splenocytes from control rats. A 5-fold enhancement of the proliferative response to mitomycin C was also seen when splenocytes from rats exposed for 10 weeks were incubated with splenocytes from nonexposed rats and additional chromium (0.1 mg chromium(VI)/L) was added to the incubation compared to the system without added chromium. It was suggested that these increased proliferative responses represent chromium-induced sensitization (Snyder and Valle 1991). Microscopic changes to lymphatic tissues, including histiocytic cellular infiltration of mesenteric and/or pancreatic nodes, were observed in rats and mice exposed to sodium dichromate dihydrate in drinking water for 3 months or 2 years (NTP 2007, 2008a). Following 3 months of exposure, histiocytic cellular infiltration was observed in male and female rats at 1.7 and 20.9 mg chromium(VI)/kg/day, respectively, and in mice at 3.1 mg chromium(VI)/kg/day (NTP 2007). After 2 years of exposure, histiocytic cellular infiltration and hemorrhage of mesenteric lymph nodes were observed in male rats at 0.77 mg chromium(VI)/kg/day (NTP 2008a). Histiocytic cellular infiltration of lymph nodes, but not hemorrhage, was observed at 2.4 mg chromium(VI)/kg/day in female rats and at 0.38 mg chromium(VI)/kg/day in mice (NTP 2008a). No abnormal histopathological changes were observed in lymphatic tissues of rats and mice exposed to oral chromium(III) (as chromium nicotinate and chromium picolinate) for 3 months or 2 years (NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). These highest doses of chromium(III) tested for intermediate and chronic exposure durations were 1,415 mg chromium(III)/kg/day as chromium picolinate in feed for 3 months and 781 mg chromium(III)/kg/day as chromium picolinate in feed for 2 years. The NOAEL and LOAEL values are recorded in

Table 3-4 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-5 and plotted in Figure 3-4 for chromium(III).

3.2.2.4 Neurological Effects

The only information regarding neurological effects in humans after oral exposure to chromium(VI) is the report of an enlarged brain and cerebral edema upon autopsy of a 14-year-old boy who died after ingesting 7.5 mg chromium(VI)/kg as potassium dichromate. These effects may be the result of accompanying renal failure (Kaufman et al. 1970). No information was identified on neurological effects in humans after oral exposure to chromium(III) compounds.

A decrease in motor activity and balance was reported in rats given 98 mg chromium(VI)/kg/day as sodium chromate in drinking water for 28 days (Diaz-Mayans et al. 1986). No additional studies were identified evaluating neurological function in laboratory animals following oral exposure to chromium(VI) or chromium(III) compounds. Histopathological examination of the brain and nervous system tissues has been evaluated in rats and mice exposed to oral chromium(VI) (as sodium dichromate dihydrate) and chromium(III) (as chromium nicotinate, chromium oxide, and chromium picolinate) for durations of 3 months to 2 years, with no abnormalities observed (Ivankovic and Preussmann 1975; NTP 2007, 2008a, 2008b; Shara et al. 2005, 2007). For chromium(VI) compounds, the highest doses tested for intermediate and chronic exposure durations were 27.9 and 8.7 chromium(VI)/kg/day, respectively, as sodium dichromate dihydrate in drinking water (NTP 2007, 2008a). For chromium(III) compounds, the highest doses tested for intermediate and chronic exposure durations were 1,806 and 2,040 mg chromium(III)/kg/day, respectively, as chromium oxide in the diet 5 days/week (Ivankovic and Preussmann 1975). None of these studies conducted more sensitive neurological, neurochemical, or neurobehavioral tests.

The NOAEL and LOAEL values are recorded in Table 3-4 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-5 and plotted in Figure 3-4 for chromium(III).

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to chromium(VI) or chromium(III) compounds.

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A number of studies have reported reproductive effects in animals orally exposed to chromium(VI). Functional and morphological effects on male reproductive organs have been reported in monkeys, rats, mice, and rabbits. In a series of studies in male bonnet monkeys (*Macaca radiata*) (Aruldas et al. 2004, 2005, 2006; Subramanian et al. 2006), decreased testes weight, histopathological changes of the epididymis, disrupted spermatogenesis, and decreased sperm count and motility were observed following exposure to 2.1, 4.1, and 8.3 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 180 days. Histopathological changes, characterized by ductal obstruction and development of microcanals, germ cell depletion, hyperplasia of Leydig cells, and Sertoli cell fibrosis, increased in severity with dose. Sperm count and motility were significantly decreased, with effects exhibiting duration- and dose-dependence (Subramanian et al. 2006). After exposure for 2 months, significant decreases in sperm count (by 13%) and motility (by 12%) were observed only in monkeys treated with 8.3 mg chromium(VI)/kg/day, whereas after 6 months, dose-dependent decreases in sperm count and motility were observed at doses of ≥ 2.1 mg chromium(VI)/kg/day. No effects on sperm count or motility were observed in monkeys treated with 1.1 mg chromium(VI)/kg/day, although histopathological assessment of male reproductive tissues was not conducted in this dose group.

Exposure of male Wistar rats to 5.2 and 10.4 mg chromium(VI)/kg/day administered as chromic acid by gavage for 6 days produced decreased sperm count and histopathological changes to the testes (Li et al. 2001). Similar effects occurred at both doses, with sperm count decreased by 75.5 and 79.6% at 5.2 and 10.4 mg chromium(VI)/kg/day, respectively, and the "level of abnormal sperm" was increased 2.4-fold and 2.8-fold at 5.2 and 10.4 mg chromium(VI)/kg/day, respectively. Histopathological assessment of testes showed decreased diameter of seminiferous tubules and germ cell rearrangement within the tubules. In contrast, exposure of F344/N male rats to chromium(VI) as sodium dichromate dihydrate in drinking water at doses up to 20.9 or mg chromium(VI)/kg/day for 3 months or 5.9 mg chromium(VI)/kg/day for 2 years did not produce histopathological changes to male reproductive tissues (NTP 2007, 2008a).

Male reproductive effects were observed in groups of 10 mature male Charles Foster strain rats administered 20, 40, and 60 mg chromium(VI)/kg/day as sodium dichromate(VI) by gavage for 90 days (Chowdhury and Mitra 1995). Testis weight, population of Leydig cells, seminiferous tubular diameter, testicular protein, DNA, and RNA were all significantly reduced at 40 and 60 mg chromium(VI)/kg/day. The number of spermatogonia was not affected by treatment; however, resting spermatocytes (high dose), pachytene spermatocytes (high dose, intermediate dose) and stage-7 spermatid (high and intermediate doses) counts were significantly reduced and were treatment related. Testicular activity of succinic dehydrogenase was significantly lowered in the two high-dose groups, testicular cholesterol

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concentrations were elevated in the highest-dosed group, and both serum testosterone and testicular levels of 3β - Δ^5 -hydroxysteroid dehydrogenase were significantly lowered. The authors also determined that the total testicular levels of ascorbic acid in the two higher-dosing groups was about twice that of the control values whereas, in the highest-treated group the total ascorbic acid levels were about half those of controls. At the low dose (20 mg/kg/day), testicular protein, 3β - Δ^5 -hydroxysteroid dehydrogenase, and serum testosterone were decreased. The authors indicated that chromium enhanced levels of the vitamin, but at the highest dose, testicular levels became exhausted, thus decreasing the ability of the cells to reduce chromium(VI).

Significant alterations in sexual behavior and aggressive behavior were observed in male Sprague-Dawley rats exposed to 42 mg chromium(VI)/kg/day as potassium dichromate in the drinking water for 12 weeks (Bataineh et al. 1997). The alterations in sexual behavior included decreased number of mounts, lower percentage of ejaculating males, and increased ejaculatory latency and postejaculatory interval. The adverse effects on aggressive behavior included significant decreases in the number of lateralizations, boxing bouts, and fights with the stud male and ventral presenting. No significant alterations in fertility were observed when the exposed males were mated with unexposed females.

Reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules were observed in BALB/c mice exposed for 7 weeks to 15.2 mg chromium(VI)/kg/day as potassium dichromate in the diet (Zahid et al. 1990). Morphologically altered sperm occurred in mice given diets providing 28 mg chromium(VI)/kg/day as potassium dichromate. No effect was found on testis or epididymis weight, and reproduction function was not assessed. In contrast, an increase in testes weight was observed in Swiss mice exposed in drinking water to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks. At the next highest dose (14 mg chromium(VI)/kg/day), decreases in seminal vesicle and preputial gland weights were observed, although no information of sperm count was reported (Elbetieha and Al-Hamood 1997). At the higher exposure level, mice consumed less water (data on water consumption were not included in the study report); thus, the daily chromium(VI) dose may be overestimated for this exposure group. In studies designed to confirm or refute the findings of the Zahid et al. (1990) study, the reproductive effects of different concentrations of chromium(VI) as potassium dichromate in the diet on BALB/c mice and Sprague-Dawley rats were investigated (NTP 1996a, 1996b). Groups of 24 of each species were fed potassium dichromate(VI) in their feed continuously for 9 weeks followed by an 8-week recovery period. For mice, the average daily ingestions of chromium(VI) were 1.05, 3.5, 7.5, and 32.2 mg/kg/day for males and for rats were 0.35, 1.05, 2.1, and 8.4 mg/kg/day (NTP 1996b). Microscopic examinations of the testes and epididymis for Sertoli nuclei and preleptotene

spermatocyte counts in stage X or XI tubules did not reveal any treatment-related effects. Similarly, exposure to sodium dichromate dihydrate in drinking water did not produce morphological changes to male reproductive organs of B6C3F1 mice exposed to 27.9 or 5.9 mg chromium(VI)/kg/day for 3 months or 2 years, respectively, or affect sperm count or motility in male B6C3F1, BALB/c and C57BL/6N mice exposed to 8.7 mg chromium(VI)/kg/day for 3 months (NTP 2007, 2008a).

Reduced sperm count and plasma testosterone were observed in male New Zealand rabbits administered 3.6 mg chromium(VI)/kg/day as potassium dichromate for 10 weeks by gavage (Yousef et al. 2006). Sperm count was decreased by 18%, total sperm output was decreased by 25.9%, total number of mobile sperm was decreased by 34.3%, and number of dead sperm increased by 23.9%. In addition, relative weight of testes and epididymis were decreased by 22.2% and plasma testosterone was decreased by 20.8%.

Effects of chromium(VI) on the female reproductive system have been reported in rats and mice. Murthy et al. (1996) reported a number of reproductive effects in female Swiss albino mice exposed to potassium dichromate in drinking water for 20 days. The observed effects included a significant reduction in the number of follicles at different stages of maturation at ≥ 60 mg chromium(VI)/kg/day, reduction in the number of ova/mice at ≥ 120 mg chromium(VI)/kg/day, significant increase in estrus cycle duration at 180 mg chromium(VI)/kg/day, and histological alterations in the ovaries (e.g., proliferated, dilated, and congested blood vessels, pyknotic nuclei in follicular cells, and atretic follicles) at ≥ 120 mg chromium(VI)/kg/day. The severity of the reproductive effects appeared to be dose-related. In an ancillary study, electron microscopy of selected ovarian tissues revealed ultrastructural changes (disintegrated cell membranes of two-layered follicular cells and altered villiform cristae of mitochondria and decreased lipid droplets in interstitial cells) in mice exposed to 1.2 mg chromium(VI)/kg/day for 90 days; the toxicological significance of these alterations is not known. The study authors suggest that the effects observed in the interstitial cells may be due to a reduction in lipid synthesizing ability, which could lead to decreased steroid hormone production. An increase in relative ovarian weight was observed in female Swiss mice exposed for 12 weeks to 14 mg chromium(VI)/kg/day as potassium dichromate (Elbetieha and Al-Hamood 1997), although the calculated daily dose may be overestimated, due to decreased water consumption in the higher concentration group (decrease was not quantified by study authors). In contrast, microscopic examinations of the ovaries showed no treatment-related effects in female BALB/c mice and Sprague-Dawley rats fed up to 9.8 and 48 mg chromium(VI)/kg/day, respectively, as potassium dichromate(VI) in the diet continuously for 9 weeks followed by an 8-week recovery period (NTP 1996b). Similarly, exposure of female F344/N rats and B6C3F1 mice to sodium

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dichromate dihydrate in drinking water at doses up to 20.9 and 27.9 mg chromium(VI)/kg/day, respectively, for 3 months or at doses up to 7.0 and 8.6 mg chromium(VI)/kg/day, respectively, for 2 years did not produce histopathological changes to the ovaries (NTP 2007, 2008a).

Several studies have reported increases in preimplantation losses and resorptions in rats and mice exposed to chromium(VI). However, for studies evaluating high concentration of chromium, it is possible that effects may, in part, be secondary to maternal toxicity. In addition, high concentration of chromium in food and water decrease palatability and can result in decreased food and drinking water consumption. Exposure of pregnant mice to 46 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in increased preimplantation and postimplantation loss, and decreased litter size. Maternal body weight gain decreased at doses ≥ 98 mg chromium(VI)/kg/day (Trivedi et al. 1989). In female Swiss albino mice exposed for 20 days prior to mating to potassium dichromate in drinking water at concentrations that resulted in doses of 0, 52, 98, or 169 mg chromium(VI)/kg/day and then mated, the number of corpora lutea was decreased at 169 mg/kg/day, preimplantation loss and resorptions were increased at ≥ 98 mg/kg/day, and placental weights were decreased at ≥ 57 mg/kg/day (Junaid et al. 1996a). Increases in the number of resorptions were also found in female Swiss albino rats exposed to 37, 70, or 87 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 20 days prior to mating (Kanojia et al. 1996). Additional reproductive effects observed at 70 or 87 mg chromium(VI)/kg/day include decreased number of corpora lutea, decreased number of implantations, and increased number of preimplantation losses. A treatment-related increase in the length of estrus cycle was significantly different from controls only in the 87 mg chromium(VI)/kg/day group. Decreased mating, decreased fertility, and increased pre- and postimplantation loss were observed in female Druckrey rats receiving doses of 45, 89, and 124 mg chromium(VI)/kg/day (as potassium dichromate in the drinking water) for 3 months prior to mating; the 89 and 124 mg chromium(VI)/kg/day groups exhibited increased resorptions as well (Kanojia et al. 1998). A decrease in fertility (decreased number of implantations and viable fetuses) was observed in male and female Swiss mice that were exposed to 6 mg chromium(VI)/kg/day as potassium dichromate for 12 weeks and then were mated with unexposed males and females; however, the classification of non-viable fetuses was not presented in this report (Elbetieha and Al-Hamood 1997). An increase in the number of mice with resorptions was also observed in the exposed females.

No reproductive effects were observed in a multigeneration reproductive assessment by continuous breeding study of BALB/c mice fed a diet containing potassium dichromate(VI). Males and females were exposed to chromium for 7 days and then 20 pairs (F_0) in each dose group were allowed to continuously

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mate for 85 days (NTP 1997). The mean doses of chromium(VI) in F₀ animals were 6.8, 13.5, and 30.0 mg/kg/day. Litters produced during the 85-day mating period were examined at postnatal day 1. There were no treatment related changes in average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time. There were no dose related gross pathological organ differences observed for both F₀ males and females, nor any differences in organ to body weight ratios. At the highest dose the F₀ females had lower mean body weights than control animals by about 7%. There were no effects on sperm number or motility, nor were there any increases in abnormal sperm morphology. Histopathological examination of livers and kidneys from F₀ males and females showed no changes that were treatment related. F₁ litters produced after 85 days were reared by the dam until weaning on postnatal day 21 then separated and allowed to mature for about 74 days. At that time, 20 pairs were allowed to mate and produce F₂ progeny. Mean exposures to chromium(VI) to F₁ animals were determined to be 7.8, 16.0, and 36.7 mg/kg/day. F₂ litters were reared by the dam until weaning on postnatal day 21 before being sacrificed. There were no differences in F₂ average litters/pair, number of live and dead pups per litter, sex ratios, pup weights, or changes in gestational time between exposed groups and controls. There were no dose-related gross pathological organ differences observed for both F₁ males and females, nor any differences in organ to body weight ratios. No histological lesions were observed in liver and kidney cells that were dose related, nor did chromium(VI) have any effects on estrous cycling.

Studies on the reproductive effects of chromium(III) yield conflicting results. Exposure to chromium(III) as chromium oxide did not cause reproductive effects in rats. Male and female rats fed 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before gestation and throughout the gestational period were observed to have normal fertility, gestational length, and litter size (Ivankovic and Preussmann 1975). A study by Bataineh et al. (1997) found significant alterations in sexual behavior (reductions in the number of mounts, increased postejaculatory interval, and decreased rates of ejaculation), aggressive behavior toward other males, and significantly lower absolute weight of testes, seminal vesicles, and preputial glands in male Sprague-Dawley rats exposed to 40 mg chromium(III)/kg/day as chromium chloride in the drinking water for 12 weeks. Male fertility indices (assessed by impregnation, number of implantations, and number of viable fetuses) did not appear to be adversely affected by exposure to chromium chloride, although the untreated females mated to treated males exhibited an increase in the total number of resorptions (Bataineh et al. 1997). In contrast, a decrease in the number of pregnant females was observed following the mating of unexposed females to male Swiss mice exposed to 13 mg chromium(III)/kg/day as chromium chloride (Elbetieha and Al-Hamood 1997). Impaired fertility (decreased number of implantations and viable fetuses) was also observed in females

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exposed to 5 mg chromium(III)/kg/day mated to unexposed males; however, no information on sperm count was reported and the definition and classification of viable fetuses were not provided (Elbetieha and Al-Hamood 1997). This study also found increased testes and ovarian weights and decreased preputial gland and uterine weights at 5 mg chromium(III)/kg/day. At lower concentrations of chromium chloride (9 mg chromium(III)/kg/day in the diet for 20 weeks), no alterations in testes or epididymis weights were observed in rats (Anderson et al. 1997b). A similar exposure to chromium(III) picolinate also did not result in testes or epididymis weight alterations (Anderson et al. 1997b). This study did not assess reproductive function. Mice exposed for 7 weeks to 9.1 mg chromium(III)/kg/day as chromium sulfate in the diet had reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules. Morphologically altered sperm occurred in BALB/c mice given diets providing 42.4 mg chromium(III)/kg/day as chromium sulfate (Zahid et al. 1990).

Exposure of rats and mice to high doses of chromium(III) compounds (chromium nicotinate and chromium picolinate) in the diet for 3 months or 2 years did not produce histopathological changes to male or female reproductive organs (NTP 2008b; Rhodes et al. 2005; Shara et al. 2005, 2007). In the 3-month studies on chromium picolinate, doses up to 505 and 506 mg chromium(III)/kg/day were evaluated in male and female F344/N rats, respectively, and doses up to 1,415 and 1,088 mg chromium(III)/kg/day were evaluated in male and female B6C3F1 mice, respectively; in the 2-year studies, doses up to 286 and 313 mg chromium(III)/kg/day were evaluated in male and female rats, respectively and doses up to 781 and 726 mg chromium(III)/kg/day, were evaluated in male and female mice, respectively (NTP 2008b; Rhodes et al. 2005). In addition, the 3-month study in rats and mice did not find any treatment-related effects on sperm count and motility or on estrous cycle (percentage of time spent in various estrous cycle stages or estrous cycle length, based on evaluation of vaginal cytology (NTP 2008b; Rhodes et al. 2005). Although the 3-month and 2-year studies on chromium nicotinate did not reveal any morphological changes to reproductive tissues of male and female Sprague-Dawley rats, only low doses were evaluated (up to 1.5 mg chromium(III)/kg/day for 3 months and up to 0.25 mg chromium(III)/kg/day for 2 years) (Shara et al. 2005, 2007).

As discussed in greater detail in Section 3.2.2.6, the reproductive system is also a target in the developing organism. Delayed vaginal opening and decreased relative weights of the uterus, ovaries, testis, seminal vesicle, and preputial glands were observed in mouse offspring exposed to potassium dichromate or chromium(III) chloride on gestational day 12 through lactation day 20 (Al-Hamood et al. 1998). Impaired fertility was observed in the chromium(III) chloride-exposed female offspring when they were

mated with unexposed males (Al-Hamood et al. 1998); no effect on fertility was observed in the male offspring.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-4 and plotted in Figure 3-3 for chromium(VI) and recorded in Table 3-5 and plotted in Figure 3-4 for chromium(III).

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to chromium or its compounds.

Several animal studies provide evidence that chromium(VI) is a developmental toxicant in rats and mice. A series of studies (Junaid et al. 1996a; Kanojia et al. 1996, 1998) were conducted to assess whether pre-mating exposure to potassium dichromate would result in developmental effects. In the first study, groups of 15 female Swiss albino mice were exposed to 0, 52, 98, or 169 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 20 days (Junaid et al. 1996a) and then mated with untreated males. At 52 mg chromium(VI)/kg/day, there was a 17.5% postimplantation loss over controls and a 30% decrease in fetal weight. At 98 mg/kg/day, there were decreases in the number of implantation sites, number of live fetuses, and fetal weight. There were also increases in the number of resorptions and number of pre- and postimplantation losses. At 169 mg chromium(VI)/kg/day, there was 100% preimplantation loss. The fetuses in the 98 mg/kg/day group had higher numbers of subdermal hemorrhagic patches and kinky short tails and decreased fetal body weight and crown rump length. Although there were no major skeletal abnormalities in any other treated animals, there was a significant reduction in ossification at 52 mg chromium(VI)/kg/day (53% compared to 12% for controls) and significant reduction in ossification in caudal, parietal and interparietal bones of fetuses at 98 mg chromium(VI)/kg/day. There were no significant soft tissue deformities in any of the treated fetuses. Although dosing occurred prior to mating, internal chromium levels remaining in females after mating may have been toxic to the conceptus that caused adverse developmental effects.

In the second study, female Swiss albino rats were exposed to potassium dichromate concentrations in the drinking water resulting in doses of 37, 70, or 87 mg chromium(VI)/kg/day for 20 days prior to mating (Kanojia et al. 1996). Lower gestational weight gain, increased postimplantation loss, and decreased number of live fetuses were observed in all treatment groups, relative to controls. Increased incidences of

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reduced fetal ossification in fetal caudal bones were reported at the 70 and 87 mg chromium(VI)/kg/day dose levels; additionally, the 87 mg chromium(VI)/kg/day dose group of fetuses exhibited increased incidences of reduced ossification in parietal and interparietal bones, as well as significant incidences of subdermal hemorrhagic thoracic and abdominal patches (42%), kinky tails (42%), and short tails (53%), relative to 0% in controls. No treatment-related gross visceral abnormalities were seen.

In the third study, groups of 10 female Druckrey rats were exposed to potassium dichromate in the drinking water for 3 months pre-mating at concentrations yielding dose levels of 45, 89, or 124 mg chromium(VI)/kg/day (Kanojia et al. 1998). Reduced maternal gestational weight gain, increased pre- and postimplantation loss, reduced fetal weight, fetal subdermal hemorrhagic thoracic and abdominal patches, increased chromium levels in maternal blood, placenta, and fetuses, and increased incidences of reduced ossification in fetal caudal bones were observed in all treatment groups. In addition, the 89 and 124 mg chromium(VI)/kg/day dose groups exhibited increased resorptions, reduced numbers of corpora lutea and fetuses per litter, reduced implantations, reduced placental weight, increased incidences of reduced ossification in fetal parietal and interparietal bones, and reduced fetal crown-rump length. No treatment-related gross visceral abnormalities were seen. A decreased number of pregnancies were observed in mated female rats administered 35.7 mg chromium(VI)/mg/day as potassium dichromate by gavage on gestational days 1–3; exposure on gestational days 4–6 decreased the number of viable fetuses and increased the number of resorptions, but did not alter the number of pregnancies (Bataineh et al. 2007).

Exposure of pregnant mice to 57 mg chromium(VI)/kg/day as potassium dichromate in drinking water during gestation resulted in embryo lethal effects (i.e., increased resorptions and increased post-implantation loss), gross abnormalities (i.e., subdermal hemorrhage, decreased cranial ossification, tail kinking), decreased crown-rump length, and decreased fetal weight. The incidence and severity of abnormalities increased at higher doses. Maternal toxicity, evidenced by decreased body weight gain, occurred at doses ≥ 120 mg chromium(VI)/kg/day. No implantations were observed in the dams given 234 mg chromium(VI)/kg/day (Trivedi et al. 1989).

Groups of 10 female Swiss albino mice received chromium(VI) as potassium dichromate in drinking water during organogenesis on days 6–14 at levels that provided 0, 53.2, 101.1, and 152.4 mg chromium(VI)/kg/day (Junaid et al. 1996b). No notable changes in behavior or clinical signs were observed in control or treated animals. Reduction of gestational weight gains of 8.2 and 30% were observed for the animals in the intermediate- and high-dose groups. The number of dead fetuses was

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higher in the high-dose group and fetal weight was lower in both intermediate- and high-dose groups (high dose=1.06 g, intermediate dose=1.14 g) as compared to the control value of 1.3 g. The number of resorption sites was 0.31 for controls, 1.00 for the low dose, 1.70 for the intermediate dose, and 2.30 for the high dose, demonstrating a dose-response relationship. The studies also showed that there was a significantly greater incidence of postimplantation loss in the two highest-dose groups of 21 and 34.60% as compared to control value of 4.32%. No significant gross structural abnormalities in any of the treated dosed groups were observed except for drooping of the wrist (carpal flexure) and subdermal hemorrhagic patches on the thoracic and abdominal regions in 16% in the offspring of the high-dose group. Significant reduced ossification in nasal frontal, parietal, interparietal, caudal, and tarsal bones were observed only in the 152.4 mg chromium(VI)/kg/day-treated animals.

Impaired development of the reproductive system was observed in the offspring of female BALB/c mice exposed to 66 mg chromium(VI)/kg/day as potassium chromate in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in vaginal opening was observed. Significant decreases in the numbers of pregnant animals, of implantations, and of viable fetuses were also observed when the female offspring were mated at age 60 days with unexposed males. No developmental effects were observed in the male offspring. Delayed vaginal opening was also reported in the offspring from rats exposed to ≥ 2.9 mg chromium(VI)/kg/day as potassium dichromate in the drinking water on postnatal days 1–21 (Banu et al. 2008; Samuel et al. 2011). These studies also reported that exposure to chromium extended the estrous cycle into diestrus; altered ovarian follicle development; decreased plasma levels of estradiol, testosterone, and progesterone; and increased follicle stimulating hormone; but did not change plasma luteinizing hormone levels. In pregnant rats exposed to 8 mg chromium(VI)/kg/day as potassium chromate in drinking water on gestational days 6 through 15, pre- and postimplantation losses and the number of resorbed and dead fetuses per litter were increased compared to controls (Elsaieed and Nada 2002). Fetal weight was significantly decreased by 67% and the number of visceral (renal pelvis dilatation) and skeletal (incomplete ossification of skull bone) anomalies per litter were significantly increased. No effects on fetal body weight or the number of fetuses per litter were observed in mice exposed to 4.8 mg chromium(VI)/kg/day as sodium dichromium dihydrate or 2.4 mg chromium(VI)/kg/day as potassium dichromate in drinking water on gestational days 0 through 18; however, no additional assessments on fetal development were conducted in this study (De Flora et al. 2006).

A series of studies have examined the effects of chromium(VI) on oxidative stress in rat offspring. Samuel et al. (2011) reported that maternal exposure to ≥ 2.9 mg chromium(VI)/kg/day as potassium

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dichromate in the drinking water on lactation days 1–21 resulted in dose-related reductions in antioxidant enzymes activities in uterine tissue from offspring measured on postnatal days 21, 45, and 65. This correlated with significant increases in lipid peroxidation and hydrogen peroxide in uterine tissue. Similar results were reported by Soudani and coworkers (Soudani et al. 2010b, 2011a, 2011b) in the kidney, liver, and bone from 14-day-old pups born to dams exposed to 9.4 mg chromium(VI)/kg/day (only dose level tested) as potassium dichromate in the drinking water on gestation days 14–21 and postnatal natal days 1–14. This dose level also caused histological alterations in the tissues studied. In all of these studies, final body weight of the pups was significantly reduced, 25% in the Soudani et al. (2010b, 2011a, 2011b) studies and 10–13% at 2.9 mg Cr/kg/day and 26–33% at 11.4 mg Cr/kg/day in the Samuel et al. (2011) study.

Chromium(VI) was also reported to alter mandibular growth and tooth eruption in rats (De Lucca et al. 2009). In this study, 4-day-old suckling pups received gavage doses of 2.2 or 4.4 mg chromium(VI)/kg/day as chromium dichromate for 10 consecutive days. High-dose rats showed significantly reduced mandibular length, base, height, and area; shorter tails; and delayed eruption of the first molar. These effects may have been secondary to a delay in body growth, as terminal body weight was reduced 20 and 40% in the low- and high-dose groups, respectively, relative to controls.

Three studies examined the developmental toxicity of chromium(III) following oral maternal exposure. In the first study, no developmental effects were observed in offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide 5 days/week for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). In contrast, reproductive effects have been observed in the offspring of mice exposed to chromium(III) chloride. Significant decreases in the relative weights of reproductive tissues (testes, seminal vesicles, and preputial glands in males; ovaries and uterus in females) were observed in the offspring of BALB/c mice exposed to 74 mg chromium(III)/kg/day as chromium(III) chloride in the drinking water on gestation day 12 through lactation day 20 (Al-Hamood et al. 1998). A significant delay in timing of vaginal opening was also noted in the female offspring. At age 60 days, the male and female offspring were mated with unexposed animals. No significant alterations in fertility (number of pregnant animals, number of implantations, number of viable fetuses, and total number of resorptions) were observed in the exposed males. A significant decrease in the number of pregnant females (62.5 versus 100% in controls) was observed among the female offspring mated with untreated males. The conflicting results between the Ivankovic and Preussmann (1975) study and the Al-Hamood et al. (1998) study may be a reflection on the developmental end points examined or the differences in the species tested. In rats administered 33.6 mg chromium(III)/kg/day (only dose tested) by

gavage as chromium chloride on gestational days 1–3, a decreased number of pregnancies were observed; however, when exposed on gestational days 4–6, no effects on pregnancy rates, implantations, viable fetuses, or resorptions were observed (Bataineh et al. 2007). Bailey et al. (2008a) reported that exposure of pregnant CD-1 mice to 25 mg chromium(III)/kg/day (only dose level tested) as chromium picolinate in the food on gestation days 6–17 did not significantly affect the number of implantations per litter, the number of resorbed or dead fetuses per litter, or fetal weight. In addition, incidences of skeletal anomalies were comparable between exposed and control groups. The same group of investigators examined neurological development in mice pups from dams exposed during gestation and lactation to 25 mg chromium(III)/kg/day as chromium picolinate (Bailey et al. 2008b). Results from a variety of tests assessing motor and sensory functions, as well as memory performed between the ages of 5 and 60 days did not show significant differences between controls, chromium-treated mice, and mice exposed to picolinic acid.

The NOAEL and LOAEL values for developmental effects in each species are recorded in [Table 3-4](#) and plotted in [Figure 3-3](#) for chromium(VI) and recorded in [Table 3-5](#) and plotted in [Figure 3-4](#) for chromium(III).

3.2.2.7 Cancer

Studies of associations between environmental exposures to chromium and cancer outcomes in humans are limited to several ecological studies (Beaumont et al. 2008; Bednar and Kies 1991; Fryzek et al. 2001; Kerger et al. 2009; Linos et al. 2011; Zhang and Li 1987). These types of studies investigate possible associations between rates of selected diseases (e.g., cancer deaths) within a geographic population and some measure of average exposure to chromium (e.g., drinking water chromium concentrations or location with respect to potential sources of exposure). Actual exposures to individuals are not determined and therefore, exposure misclassification bias often contributes to uncertainty regarding associations between outcomes and exposure. Findings from ecological studies are mixed and do not strongly support associations between cancer mortality and exposures to chromium. One study did find significantly higher stomach cancer death rates in areas where well water chromium levels had been elevated (Beaumont et al. 2008).

An ecological study of an area near a ferrochromium production plant in the Liaoning Province, China compared cancer mortality in locations that had relatively high or low chromium concentrations in well water (Zhang and Li 1987). The briefly reported study (Zhang and Li 1987) found increases in the

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mortality rates from lung cancer (13.17–21.39/100,000 compared to 11.21/100,000 for the entire Taihe district) and stomach cancer (27.68–55.17/100,000; comparison value not reported); however, no statistical analyses were reported. Beaumont et al. (2008) re-analyzed the cancer mortality data from this population and estimated cancer mortality rates (cancers deaths per person-year in an 8-year observation period) based on mortality records for the period 1970–1978. The province was divided into nine areas, four of which were designated as no (or low) chromium (groundwater concentration <0.001 mg Cr/L) and five which were designated as high chromium. The main sources of chromium in well water were from discharges from the plant to surface water and groundwater, which began operating in 1961. Chromium levels in well water from samples collected in the contaminated areas in 1965 (by this time, full-scale production was occurring) ranged from 0.6 to 20 mg/L with 15% of wells having concentrations >2 mg/L. Total number of cancer deaths were 80 (of 98,458 person-years) in the high chromium areas and 182 (of 252,277 person-years) in the comparison areas. Age-adjusted cancer mortality rate ratios (rate in high regions/rate in low regions) were 1.82 (95% CI 1.11–2.91) for stomach cancer, 1.15 (95% CI 0.62–2.05) for lung cancer, 0.86 (95% CI 0.53–1.36) for other cancers, and 1.13 (95% CI 0.86–1.46) for all cancer. In a subsequent re-analysis of the cancer mortality data, Kerger et al. (2009) divided the population into three groups: residents of the industrial town of TangHeZi, residents of three agricultural villages without chromium(VI) groundwater contamination, and residents of five agricultural villages with chromium(VI) groundwater contamination. The relative risks of lung and stomach cancers were similar for the chromium-exposed residents and residents of agricultural villages without chromium contamination, and no associations were found between average chromium concentration in the drinking water and stomach and lung cancer rates. However, stomach cancer was higher in the residents of both agricultural groups when compared to TangHeZi residents.

An ecological study of areas in Kings County and San Bernardino County, California compared cancer mortality in locations near natural gas compressor plants with areas not located near the plants (Fryzek et al. 2001). Hexavalent chromium compounds had been used as additives in cooling tower water at the gas plants during the period 1950 to approximately 1980. Mortality records for zip codes for the cities of Kettleman City (in Kings County), and Hinkely and Topock (in San Bernardino County), in which natural gas compressor plants were located, were compared to records from zip codes in Kings County and San Bernardino County, other than those encompassing these three cities. The study included mortality records for the period 1989–1998, during which time 2,226,214 deaths were recorded. Age-adjusted cancer mortality rate ratios (rate in areas near the plant/rate in comparison areas) were 1.03 (95% CI 0.90–1.17) for lung cancer death, 0.93 (95% CI 0.87–1.00) for all cancer deaths, and 0.98 (95% CI 0.95–1.02) for all deaths.

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An ecological study compared levels of chromium (and other chemicals) in drinking water in 453 Nebraska communities with death rates in these areas (Bednar and Kies 1991). Data on chromium in drinking water were obtained for the year period 1986–1987, and mortality data was obtained for the year 1986. Mean chromium concentration in drinking water was 0.002 mg/L (range <0.001–0.01). Linear correlation (Pearson) between chromium levels and death from chronic lung disease was -0.101 ($p=0.03$).

A study of an area of Greece with elevated chromium(VI) levels in the public drinking water supply found significantly higher SMRs for primary liver cancer (SMR=1104.2; 95% CI=403.2–2403.3), lung cancer (SMR 145.1; 95% CI=100.5–202.8), and cancer of the kidney and other genitourinary organs among women (SMR=367.8; 95% CI=119.4–858.3) (Linós et al. 2011). Chromium levels in the drinking water ranged from 8.3 to 51 µg/L.

Chronic exposure to chromium(VI) as sodium dichromate in drinking water resulted in increased incidence of neoplasms of the digestive tract in mice and rats (NTP 2008a). Groups of 50 male and 50 female F344/N rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for 2 years. NTP (2008a) calculated 2-year mean daily doses of 0, 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg/day (equivalent to 0, 0.21, 0.77, 2.1 or 5.9 mg chromium(VI)/kg/day) in male rats and, 0, 0.7, 2.7, 7, or 20 mg sodium dichromate dihydrate/kg/day (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day) in female rats. Incidences of squamous epithelial neoplasms of the oral mucosa and tongue were elevated in rats exposed to sodium dichromate compared to controls, with significant increased mortality-adjusted incidence in males at the 5.9 mg chromium(VI)/kg/day dose (15.7 versus 0% in controls, $p=0.007$), and in females at the 7.0 mg chromium(VI)/kg/day (23.9 versus 2.2% in controls, $p<0.001$). In both male and female rats, there was a significant dose trend for digestive tract neoplasms ($p<0.001$). Groups of 50 male B6C3F1 mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L, and 50 female B6C3F1 mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated 2-year mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7 or 17 mg/kg/day (equivalent to 0, 0.38, 0.91, 2.4 and 5.9 mg chromium(VI)/kg/day); and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg/day (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day). Incidences of neoplasms of the of the small intestine (duodenum, jejunum, or ileum) were elevated in mice exposed to sodium dichromate compared to controls, with significant increased mortality-adjusted incidence in males at the 2.4 (15.1 versus 2.2% in controls, $p=0.032$) or 5.9 mg chromium(VI)/kg/day dose (43.8 versus 2.2% in controls, $p=0.001$), and in females at the 3.1 (36.3 versus 2.2% in controls) or

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8.7 mg chromium(VI)/kg/day (45.9 versus 2.2% in controls, $p < 0.001$). In both male and female mice, there was a significant dose trend for digestive tract neoplasms ($p < 0.001$). NTP (2008a) concluded that the results of these studies provided clear evidence of carcinogenic activity of sodium dichromate dihydrate in male and female F344/N rats based on increased incidences of squamous cell neoplasms of the oral cavity; and clear evidence of carcinogenic activity of in male and female B6C3F1 mice based on increased incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum).

The carcinogenicity of chromium(VI) was evaluated in mice exposed to potassium chromate in drinking water at 9 mg chromium(VI)/kg/day for three generations (880 days) (Borneff et al. 1968). In treated mice, 2 of 66 females developed forestomach carcinoma and 9 of 66 females and 1 of 35 males developed forestomach papilloma. The vehicle controls also developed forestomach papilloma (2 of 79 females, 3 of 47 males) but no carcinoma. The incidence of forestomach tumors in the treated mice was not significantly higher than controls. Although study authors concluded that evidence of carcinogenicity was equivocal, statistical analysis of these data (performed by Syracuse Research Corporation) using Fischer's exact test shows statistically significant increases in the incidence of adenoma or carcinomas (forestomach) ($p = 0.0067$) and in the incidence of adenomas (forestomach) alone ($p = 0.027$), compared to control. In this same study, coexposure to both potassium chromate and 3,4-benzpyrene in a similar protocol showed that potassium chromate did not potentiate the carcinogenicity of 3,4-benzpyrene (Borneff et al. 1968). Exposure of female hairless mice to ultraviolet light in combination with chromium(VI) as potassium chromate in drinking water at concentrations of 2.5 or 5.0 mg potassium chromate(VI)/L (approximately 0.18, or 0.35 mg chromium(VI)/kg/day) for 182 days, or in the diet at concentrations of 0, 2.5, or 5.0 mg potassium chromate(VI)/kg food (approximately 0.13, or 0.26 mg chromium(VI)/kg/day) for 26 weeks, produced an increased incidence of skin tumors compared to animals exposed to UV light alone or chromium(VI) alone (Davidson et al. 2004; Uddin et al. 2007). Exposure to chromium(VI) alone did not result in neoplasms.

Chronic exposure to chromium(III) as chromium picolinate dihydrate in the diet resulted in increased incidence of neoplasms of the preputial gland in male rats; however, no increased neoplasms were observed in female rats, or in male or female mice (NTP 2008b). Groups of 50 male and 50 female F344/N rats were fed a diet containing 0, 2,000, 10,000, or 50,000 ppm chromium picolinate monohydrate for 2 years. NTP (2008b) calculated 2-year mean daily doses of chromium picolinate monohydrate of 0, 90, 460, and 2,400 mg/kg/day (equivalent to 0, 11, 55, or 286 mg chromium(III)/kg/day) in male rats and 0, 100, 510, and 2,630 mg/kg/day (equivalent to 0, 12, 61, or 313 mg chromium(III)/kg/day) in female rats. Mortality-adjusted incidence of adenoma of the preputial gland of

male rats was significantly elevated in rats that received 55 mg chromium(III)/kg/day (14.9 versus 2.2% in controls, $p=0.031$), but not in rats exposed to lower dose or the higher dose (286 mg chromium(III)/kg/day), and there was no significant dose trend for the neoplasm. Incidences of neoplasms were not significantly different from controls in females, including neoplasms of the clitoral gland. Groups of 50 male and 50 female F6C3F1 mice were fed a diet containing 0, 2,000, 10,000, or 50,000 ppm chromium picolinate monohydrate for 2 years. NTP (2008b) calculated 2-year mean daily doses of chromium picolinate monohydrate of 0, 250, 1,200, and 6,565 mg/kg/day (equivalent to 0, 30, 143, 2.1, or 781 mg chromium(III)/kg/day) in male mice and 100, 510, and 2,630 mg/kg/day (equivalent to 0, 29, 143, or 726 mg chromium(III)/kg/day) in female mice. No neoplasms or lesions were attributed to exposure to chromium picolinate monohydrate in male or female mice. NTP (2008b) concluded that evidence for carcinogenicity of chromium picolinate in male rats was equivocal and that the study provided no evidence of carcinogenicity in mice.

No evidence of carcinogenicity was observed in male or female rats fed diets containing chromium oxide at 2,040 mg chromium(III)/kg/day 5 days/week for 2 years. Moreover, no evidence of carcinogenicity was found in the offspring of these rats after 600 days of observation (Ivankovic and Preussmann 1975).

The Cancer Effect Levels (CELs) for chromium(VI) are recorded in [Table 3-4](#) and plotted in [Figure 3-3](#).

3.2.3 Dermal Exposure

Some chromium(VI) compounds, such as chromium trioxide (chromic acid), potassium dichromate, potassium chromate, sodium dichromate, and sodium chromate, are very caustic and can cause burns upon dermal contact. These burns can facilitate the absorption of the compound and lead to systemic toxicity.

3.2.3.1 Death

A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred following the treatment with the chromium(VI) compounds. Death occurred 4 weeks after exposure (Major 1922). Twelve individuals died as a result of infection to necrotic areas of the skin that were caused by application of a salve made up with potassium chromate used to treat scabies. Renal failure was observed. Autopsies revealed fatty degeneration of the heart, hyperemia and necrosis of kidney tubules, and hyperemia of the gastric mucosa (Brieger 1920).

Single-dose dermal LD₅₀ values in New Zealand rabbits exposed to chromium(VI) as sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate were determined by Gad et al. (1986). LD₅₀ values ranged from 361 to 553 mg chromium(VI)/kg for females and from 336 to 763 mg chromium(VI)/kg for males. Signs of toxicity included dermal necrosis, eschar formation, dermal edema and erythema, diarrhea, and hypoactivity. The dermal LD₅₀ value for chromium trioxide was 30 mg chromium(VI)/kg for combined sexes (American Chrome and Chemicals 1989). In male and female Sprague-Dawley rats, no mortalities were observed following a single dermal application of 621.6 mg chromium(III)/kg as chromium nicotinate (Shara et al. 2005).

The LD₅₀ values are recorded in [Table 3-6](#) for chromium(VI) and [Table 3-7](#) for chromium(III).

3.2.3.2 Systemic Effects

Several reports of health effects in individuals treated with potassium dichromate are discussed below (Brieger 1920; Major 1922; Smith 1931). The results of these studies should be interpreted cautiously because pre-existing conditions may have contributed to the observed effects. The highest NOAEL value and all reliable LOAEL values for dermal effects in each species and duration category are recorded in [Table 3-6](#) for chromium(VI) and [Table 3-7](#) for chromium(III).

Respiratory Effects. Occupational exposure to chromium compounds results in direct contact of mucocutaneous tissue, such as nasal and pharyngeal epithelium, due to inhalation of airborne dust and mists of these compounds. Such exposures have led to nose and throat irritation and nasal septum perforation. Because exposure is to airborne chromium, studies noting these effects are described in Section 3.2.1.2.

A case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months noted that he also had breathing difficulties. However, because he also had many previous attacks of hay fever and asthma, it was not possible to distinguish whether his breathing difficulties were caused by or exacerbated by dermal exposure to ammonium dichromate (Smith 1931). In another case report, dyspnea followed by acute pulmonary edema with subsequent respiratory failure was reported in an electroplating worker exposed to chromic acid on the legs for approximately 10 minutes while cleaning a tank (Lin et al. 2009).

Table 3-6 Levels of Significant Exposure to Chromium VI - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Serious	Reference		Comments
				Less Serious			Chemical Form		
ACUTE EXPOSURE									
Death									
Rabbit (Fischer- 344)	24 hr					30 mg/kg	(LD50)	American Chrome and Chemicals 1989 CrO3 (VI)	
Rabbit (New Zealand)	once					763 M mg/kg	(LD50)	Gad et al. 1986 (NH4)2Cr2O7 (VI)	
						549 F mg/kg	(LD50)		
Rabbit (New Zealand)	once					403 M mg/kg	(LD50)	Gad et al. 1986 K2Cr2O7 (VI)	
						490 F mg/kg	(LD50)		
Rabbit (New Zealand)	once					336 M mg/kg	(LD50)	Gad et al. 1986 Na2Cr2O7·2H2O (VI)	
						361 F mg/kg	(LD50)		
Rabbit (New Zealand)	2 d					426 M mg/kg	(LD50)	Gad et al. 1986 Na2CrO4 (VI)	
						553 F mg/kg	(LD50)		

Table 3-6 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Systemic Rat (NS)	once	Hepatic		0.175 (altered carbohydrate Percent (%) metabolism)		Merkur'eva et al. 1982 K2Cr2O7 (VI)	
				0.175 (dermatitis) Percent (%)			
Gn Pig (albino)	once	Dermal			1.9 M mg/kg (skin corrosion)	Samitz 1970 K2Cr2O7 (VI)	
Gn Pig (NS)	3 d 1 x/d	Dermal		0.35 mg/kg (skin ulcers)		Samitz and Epstein 1962 K2Cr2O7 (VI)	
Rabbit (NS)	5 min or 24 hr	Ocular	0.1 M ml			Fujii et al. 1976 Na2CrO4 and Na2Cr2O7 (VI)	
Rabbit (New Zealand)	4 hr	Dermal		55 mg/kg (necrosis, erythema, edema)		Gad et al. 1986 (NH4)2Cr2O7 (VI)	
Rabbit (New Zealand)	4 hr	Dermal		47 M mg/kg (erythema, edema, necrosis)		Gad et al. 1986 K2Cr2O7 (VI)	
Rabbit (New Zealand)	4 hr	Dermal		47 M mg/kg (necrosis, erythema, edema)		Gad et al. 1986 Na2Cr2O7 (VI)	

Table 3-6 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Serious	Reference Chemical Form	Comments
			NOAEL	Less Serious			
Rabbit (New Zealand)	4 hr	Dermal		42 M mg/kg (erythema, edema)		Gad et al. 1986 Na ₂ CrO ₄ (VI)	
Immunolymphoret Human	once			0.175 Percent (%) (positive patch test)		Engelbrigtsten 1952 K ₂ Cr ₂ O ₇ (VI)	
Human	48 hr			0.001 Percent (%) (increased skin thickness and blood flow)		Eun and Marks 1990 K ₂ Cr ₂ O ₇ (VI)	
Human	48 hr (NS)			1 B mg/L (positive patch test)		Hansen et al. 2003 K ₂ Cr ₂ O ₇ (VI)	
Human	48 hr			0.18 Percent (%) (positive patch test)		Hansen et al. 2006b K ₂ Cr ₂ O ₇ (VI)	
Human	48 hr			0.26 M Percent (%) (erythema)		Levin et al. 1959 CrO ₃ (VI)	
Human	once		0.0013 µg/mm ²	0.0026 µg/mm ² (positive patch test)		Mali et al. 1966 K ₂ Cr ₂ O ₇ (VI)	
Human	once			0.018 µg/cm ² (positive patch test)		Nethercott et al. 1994 K ₂ Cr ₂ O ₇ (VI)	

Table 3-6 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Human	2 d			0.175 Percent (%) (positive patch test)		Newhouse 1963 K ₂ Cr ₂ O ₇ (VI)	
Human	48 hr			0.175 Percent (%) (chromium allergy)		Peltonen and Fraki 1983 K ₂ Cr ₂ O ₇ (VI)	
Human	once			0.09 mg (erythema)		Samitz and Shrager 1966 K ₂ Cr ₂ O ₇ (VI)	
Human	once			0.09 Percent (%) (positive patch test)		Wahba and Cohen 1979 K ₂ Cr ₂ O ₇ (VI)	
Human	once			0.09 Percent (%) (positive patch test)		Winston and Walsh 1951 Na ₂ Cr ₂ O ₇ (VI)	
Gn Pig (albino)	once			0.009 mg/kg (contact sensitivity)		Gross et al. 1968 K ₂ Cr ₂ O ₇ (VI)	
Gn Pig (NS)	once			0.04 F mg/kg (erythematic reaction)		Jansen and Berrens 1968 K ₂ Cr ₂ O ₇ (VI)	

Table 3-6 Levels of Significant Exposure to Chromium VI - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference	Comments
				Less Serious	Serious		
INTERMEDIATE EXPOSURE							
Immuno/ Lymphoret							
Mouse	18 d			0.35 (contact sensitivity)		Mor et al. 1988	
(BALB/c or ICR)				Percent (%)		K2Cr2O7 (VI)	
CHRONIC EXPOSURE							
Systemic							
Human	>1 yr (occup)	Dermal		0.03 M (ulcerated skin)		Gibb et al. 2000a	
				mg/m³		CrO3 (VI)	
				0.029 M (dermatitis)			
				mg/m³			
				0.027 M (burn)			
				mg/m³			
				0.025 M (irritated skin)			
				mg/m³			
Human	7.5 yr avg (range 3-16 yr) (occup)	Resp		0.004 M (nasal septum ulceration and perforation)		Lucas and Kramkowski 1975	
				mg/m³		CrO3 (VI)	
		Gastro		0.004 M (possible gastritis, ulcers)			
				mg/m³			
		Dermal		0.005 M (chrome holes)			
				mg/m³			

avg = average; d = day(s); F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; x = times; yr = year(s)

avg = average; d = day(s); F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; hr = hour(s); Immunolymphoretic = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; x = times; yr = year(s)

Table 3-7 Levels of Significant Exposure to Chromium III - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference	Comments
				Less Serious	Serious		
ACUTE EXPOSURE							
Systemic							
Gn Pig (NS)	3 d 1 x/d	Dermal	1 mg/kg			Samitz and Epstein 1962 Cr2(SO4)3 (III)	
Immuno/ Lymphoret							
Human	48 hr			0.37 Percent (%)	(positive patch test)	Fregert and Rorsman 1964 CrCl3.6H2O (III)	
Human	48 hr (NS)			6 B mg/L	(positive patch test)	Hansen et al. 2003 CrCl3.6H2O (III)	
Human	48 hr			3.7 Percent (%)	(positive patch test)	Hansen et al. 2006b CrCl3 (III)	
Human	once			0.16 µg/mm2	(positive patch test)	Mali et al. 1966 CrCl3 (III)	
Human	once		33 µg/cm²			Nethercott et al. 1994 CrCl3 (III)	
Human	once			0.33 mg	(erythema)	Samitz and Shrager 1966 Cr2(SO4)3 (III)	
Human	once			0.08 mg	(erythema)	Samitz and Shrager 1966 CrCl3 (III)	

Table 3-7 Levels of Significant Exposure to Chromium III - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Serious	Reference Chemical Form	Comments
				Less Serious				
Gn Pig (albino)	once			0.004 mg/kg	(erythematic reaction)		Gross et al. 1968 CrCl3 (III)	
Gn Pig (NS)	once			0.03 F mg/kg	(erythematic reaction)		Jansen and Berrens 1968 Cr2(SO4)3 (III)	

B = both sexes; d = day(s); F = female; Gn Pig = guinea pig; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level;
 NOAEL = no-observed-adverse-effect level; NS = not specified; x = times

No studies were located regarding respiratory effects in animals after dermal exposure to chromium or its compounds.

Cardiovascular Effects. Information regarding cardiovascular effects in humans after dermal exposure to chromium or its compounds is limited. Weak, thready, and markedly dicrotic pulse developed ≈ 1.5 hours after a salve made up with potassium chromate to treat scabies was applied to skin of an unspecified number of individuals. Some of the people died as a result of infection to the exposed area, and autopsy revealed degeneration of the heart (Brieger 1920).

No studies were located regarding cardiovascular effects in animals after dermal exposure to chromium or its compounds.

Gastrointestinal Effects. Vomiting occurred soon after application of a salve made up of potassium chromate to the skin of an unspecified number of individuals for the treatment of scabies. Some of these individuals died as a result of infection of the exposed area, and autopsy revealed hyperemia of the gastric mucosa (Brieger 1920). Nausea, vomiting, and abdominal pain were reported by an electroplating worker dermally exposed to chromic acid for approximately 10 minutes (Lin et al. 2009).

Diarrhea was reported in New Zealand rabbits exposed to lethal concentrations of chromium(VI) compounds (Gad et al. 1986).

Hematological Effects. Severe leukocytosis, with notable increases in immature polymorphonuclear cells, myelocytes, and myeloblasts and nucleated red cells and Howell-Jolly bodies, indicative of hemolytic anemia were observed in individuals after application of a salve that contained potassium chromate to treat scabies (Brieger 1920). Leukocytosis was also described in a case report of a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months (Smith 1931) and in an electroplating worker exposed on the legs to chromic acid for approximately 10 minutes; anemia and thrombocytopenia developed 5 days postexposure (Lin et al. 2009).

No studies were located regarding hematological effects in animals after dermal exposure to chromium compounds.

Musculoskeletal Effects. Information regarding musculoskeletal effects in humans after dermal exposure to chromium or its compounds is limited to a case report. A man was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment, where he had worked for a few months. He also had tenderness and edema of the muscles of the extremities (Smith 1931).

No studies were located regarding musculoskeletal effects in animals after dermal exposure to chromium or its compounds.

Hepatic Effects. No reliable studies were located regarding hepatic effects in humans after dermal exposure to chromium compounds.

Information regarding liver effects in animals after dermal exposure to chromium or its compounds is limited. A single application of 0.5% potassium dichromate (0.175% chromium(VI)) to the shaved skin of rats resulted in increased levels of serotonin in the liver, decreased activities of acetylcholinesterase and cholinesterase in the plasma and erythrocytes, increased levels of acetylcholine in the blood, and increased glycoprotein hexose in the serum. These effects may indicate alterations in carbohydrate metabolism (Merkur'eva et al. 1982). Application of 50 mg chromium/kg/day (specific chemical or valence state not reported) for 30 days to clipped skin under occluded conditions to female guinea pigs produced small increases in enzyme activities in liver tissue, specifically aspartate aminotransferase (17%), alanine aminotransferase (2%), acid phosphatase (16%), and gamma glutamyl transpeptidase (54%), compared to untreated controls (Mathur 2005). Microscopic evaluation of the liver showed “shrunk” hepatocytes and thickening of the walls of hepatic arteries.

Renal Effects. Acute nephritis with albuminuria and oliguria, polyuria, and nitrogen retention were observed in individuals after application of a salve that contained potassium chromate. These effects disappeared in individuals who survived. Autopsy of people who died revealed hyperemia and tubular necrosis (Brieger 1920). Acute nephritis with polyuria and proteinuria were also described in a man who was admitted to a hospital with skin ulcers on both hands due to dermal exposure to ammonium dichromate in a planographic printing establishment where he had worked for a few months (Smith 1931). A 49-year-old man with an inoperable carcinoma of the face was treated with chromic acid crystals. Severe nephritis occurred after treatment with the chromium(VI) compound. Urinalysis revealed marked protein in the urine. Death resulted 4 weeks after exposure. A postmortem examination of the kidneys revealed extensive destruction of the tubular epithelium (Major 1922). Similarly, oliguria with increasing

serum creatinine levels were observed within 24 hours in an electroplating worker dermally exposed on the legs to chromic acid for approximately 10 minutes; the kidney damage progressed to acute renal failure (Lin et al. 2009).

Application of 50 mg chromium/kg/day (specific chemical or valence state not reported) for 30 days to clipped skin under occluded conditions to female guinea pigs produced increases in enzyme activities in renal tissue, specifically asparatate aminotransferase (8%), alanine aminotransferase (96%), and acid phosphatase (4%), compared to untreated controls (Mathur 2005). Microscopic evaluation of the kidney showed lobularization of the glomerular tuft and congestion of capillaries. No additional information on renal effects of dermal exposure to chromium(VI) or chromium(III) compounds was identified.

Dermal Effects. Occupational exposure to airborne chromium compounds has been associated with effects on the nasal septum, such as ulceration and perforation. These studies are discussed in Section 3.2.1.2 on Respiratory Effects. Dermal exposure to chromium compounds can cause contact allergic dermatitis in sensitive individuals, which is discussed in Section 3.2.3.3. Skin burns, blisters, and skin ulcers, also known as chrome holes or chrome sores, are more likely associated with direct dermal contact with solutions of chromium compounds, but exposure of the skin to airborne fumes and mists of chromium compounds may contribute to these effects.

Acute dermal exposure of humans to chromium(VI) compounds causes skin burns. Necrosis and sloughing of the skin occurred in individuals at the site of application of a salve containing potassium chromate. Twelve of 31 people died as a result of infection of these areas (Brieger 1920). In another case, a man who slipped at work and plunged his arm into a vat of chromic acid had extensive burns and necrosis on his arm (Cason 1959). Multiple skin ulcers were observed in an electroplating worker exposed on the legs to chromic acid for approximately 10 minutes (Lin et al. 2009).

Longer-term occupational exposure to chromium compounds in most chromium-related industries can cause deep penetrating holes or ulcers on the skin. A man who had worked for a few months in a planographic printing establishment, where he handled and washed sheets of zinc that had been treated with a solution of ammonium dichromate, had skin ulceration on both hands (Smith 1931).

In an extensive survey to determine the health status of chromate workers in seven U.S. chromate production plants, 50% of the chromate workers had skin ulcers or scars. In addition, inflammation of oral structures, keratosis of the lips, gingiva, and palate, gingivitis, and periodontitis due to exposure of

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these mucocutaneous tissues to airborne chromium were observed in higher incidence in the chromate workers than in controls. Various manufacturing processes in the plants resulted in exposure of workers to chromite ore (mean time-weighted concentration of 0–0.89 mg chromium(III)/m³ air); water-soluble chromium(VI) compounds (0.005–0.17 mg chromium(VI)/m³); and acid-soluble/water-insoluble chromium compounds (including basic chromium sulfate), which may or may not entirely represent chromium(III) (0–0.47 mg chromium/m³ air) (PHS 1953). Among 258 electroplating workers exposed to chromium trioxide fumes at 0.1 mg chromium(VI)/m³ for <1 year, 5% developed dental lesions, consisting of yellowing and wearing down of the teeth (Gomes 1972).

Chronic exposure of chrome chemical production workers produced dermal symptoms, including irritated and ulcerated skin, dermatitis, and burns (Gibb et al. 2000a). Medical records of 2,307 male workers employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker was the annual mean in the area of employment during the year of first diagnosis). Ulcerated skin occurred in 31.6% of workers, at a mean exposure of 0.029 mg Cr(VI)/m³ and a mean time to first diagnosis of 373 days. Ulcerated skin was significantly associated with chromium(VI) exposure ($p=0.004$), with a relative risk of 1.11. Burns were observed in 31.4% of workers, with a mean exposure and time to onset of 0.027 mg/m³ and 409 days, respectively. Dermatitis was observed in 18.5% of workers, with a mean exposure and time to onset of 0.029 mg/m³ and 624 days, respectively. Irritated skin was observed in 15.1% of workers, with a mean exposure and time to onset of 0.025 mg/m³ and 719 days, respectively.

Irritation and ulceration of the buccal cavity, as well as chrome holes on the skin, were also observed in workers in a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes (Lieberman 1941). Electroplaters in Czechoslovakia exposed to an average of 0.414 mg chromium(VI)/m³ above the plating baths also had high incidences of buccal cavity changes, including chronic tonsillitis, pharyngitis, and papilloma (Hanslian et al. 1967). In a study of 303 electroplating workers in Brazil, whose jobs involve working with cold chromium trioxide solutions, >50% had ulcerous scars on the hands, arms, and feet. Air monitoring revealed that most workers were exposed to ≥ 0.1 mg chromium(VI)/m³, but even those exposed to <0.1 mg chromium(VI)/m³ developed lesions (Gomes 1972). Chrome holes were also noted at high incidence in chrome platers in Singapore, while controls had no skin ulcers (Lee and Goh 1988). The incidence of skin ulcers was significantly increased in a group of 997 chrome platers compared with 1,117 controls. The workers had been exposed

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to chromium(VI) in air and in dust. The air levels were generally <0.3 mg chromium(VI)/m³, and dust levels were generally between 0.3 and 97 mg chromium(VI)/g (Royle 1975b). In a NIOSH Health Hazard Evaluation of an electroplating facility in the United States, seven workers reported past history of skin sores, and nine had scars characteristic of healed chrome sores. The workers had been employed for an average of 7.5 years and were exposed to a mean concentration of 0.004 mg chromium(VI)/m³ in air. In addition, spot tests showed widespread contamination of almost all workroom surfaces and hands (Lucas and Kramkowski 1975).

An early report of cases of chrome ulcers in leather tanners noted that the only workmen in tanneries who suffered chrome holes were those who handled dichromate salts. In one of these cases, the penetration extended into the joint, requiring amputation of the finger (Da Costa et al. 1916). In a medical survey of a chemical plant that processed chromite ore, 198 of 285 workers had chrome ulcers or scars on the hands and arms. These workers had been exposed to one or more chromium(VI) compounds in the form of chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, and ammonium dichromate (Edmundson 1951).

Similar dermal effects have been observed in animals. Dermal application of chromium(VI) compounds to the clipped, nonabraded skin of rabbits at 42–55 mg/kg resulted in skin inflammation, edema, and necrosis. Skin corrosion and eschar formation occurred at lethal doses (see Section 3.2.3.1) (Gad et al. 1986). Application of 0.01 or 0.05 mL of 0.34 molar solution of potassium dichromate (0.35 mg chromium(VI) or 1.9 mg chromium(VI)/kg) to the abraded skin of guinea pigs resulted in skin ulcers (Samitz 1970; Samitz and Epstein 1962). Similar application of 0.01 mL of a 1 molar solution of chromium sulfate (1 mg chromium(III)/kg) however, did not cause skin ulcers in guinea pigs (Samitz and Epstein 1962). In a primary dermal irritation test, application of 88 mg chromium(III) as chromium nicotinate in corn oil to clipped skin of male and female New Zealand albino rabbits produced very slight erythema after 1 hour after application, with no signs of dermal irritation 48 hours after application (Shara et al. 2005).

Dermal sensitization due to hypersensitivity to chromium is discussed in Section 3.2.3.3.

Ocular Effects. Medical records of 2,307 male workers employed at a chromate production plant in Baltimore, Maryland between 1950 and 1974 were evaluated to determine the percentage of workers reporting clinical symptoms, mean time of employment to first diagnosis of symptoms, and mean exposure to chromium(VI) at the time of first diagnosis (exposure for each worker

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was the annual mean in the area of employment during the year of first diagnosis) (Gibb et al. 2000a). Conjunctivitis was reported on 20.0% of the study population, at a mean exposure level of 0.025 mg Cr(VI)/m³ and a mean time-to-onset of 604 days.

Direct contact of the eyes with chromium compounds also causes ocular effects. Corneal vesication was described in a worker who accidentally got a crystal of potassium dichromate or a drop of a potassium dichromate solution in his eye (Thomson 1903). In an extensive study of chromate workers in seven U.S. chromate production plants, eyes were examined because accidental splashes of chromium compounds into the eye had been observed in these plants. Congestion of the conjunctiva was found in 38.7% of the 897 workers, discharge in 3.2%, corneal scarring in 2.3%, any abnormal finding in 40.8%, and burning in 17.0%, compared with respective frequencies of 25.8, 1.3, 2.6, 29.0, and 22.6% in 155 nonchromate workers. Only the incidences of congestion of the conjunctiva and any abnormal findings were significantly higher in the exposed workers than in the controls (PHS 1953).

Instillation of 0.1 mL of a 1,000 mg chromium(VI)/L solution of sodium dichromate and sodium chromate (pH 7.4) was not irritating or corrosive to the eyes of rabbits (Fujii et al. 1976). Histological examination of the eyes of rats exposed to chromium dioxide (15.5 mg chromium(IV)/m³) in air revealed no lesions (Lee et al. 1989). In a primary eye irritation test, direct conjunctival instillation of 5.2 mg chromium(III) as chromium nicotinate in water to male and female New Zealand albino rabbits produced conjunctivitis within 1 hour of application, although no corneal opacity or iritis was observed (Shara et al. 2005).

3.2.3.3 Immunological and Lymphoreticular Effects

In addition to the irritating and ulcerating effects, direct skin contact with chromium compounds elicits an allergic response, characterized by eczema or dermatitis, in sensitized individuals. Chromium-induced allergic contact dermatitis is typically isolated to areas at the site of contact, rarely occurring in areas remote to the point of contact (Winder and Carmody 2002). Following an induction phase during which the patient becomes sensitized, subsequent dermal exposure results in an allergic response. The acute response phase lasts for a few days to a few weeks and is characterized by erythema, edema, and small and large blisters; the chronic phase exhibits similar clinical features, but may also include thickened, scaly, and fissured skin (Winder and Carmody 2002). Evaluation by light and electron microscopy of skin biopsies of individuals with active dermatitis due to chromium shows increased intracellular edema

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of lower epidermal keratinocytes, formation of vacuoles in cells of the lower epidermis and dendritic, spindle-shaped cells in the upper dermis (Shah and Palmer 2002).

Studies using dermal patch testing as a technique to diagnose chromium sensitivity show that challenge with small amounts of chromium(VI) or chromium(III) can induce a response in sensitized individuals. A series of studies conducted by Hansen et al. (2003, 2006a, 2006b) show that patients with chromium-induced dermatitis associated with exposure to leather products responded to both low-dose and high-dose chromium(VI) and chromium(III) challenge using skin patch tests. In a group of 18 patients previously diagnosed with chromium sensitivity, the concentration of chromium(VI) as potassium dichromate required to elicit a positive response on skin patch challenge was 6 mg chromium(VI)/L and 1 mg chromium(III)/L as chromium trichloride (Hansen et al. 2003). Using higher doses in 2,211 patients with suspected contact dermatitis, 71 (3.2%) tested positive to 0.5% potassium dichromate (0.18% chromium(VI)) on skin patch challenge; of these 71 chromium(VI)-positive patients, 31 also produce a positive result when challenged with 13% chromium trichloride (3.7% chromium(III)) (Hansen et al. 2006b). The positive response to both chromium(VI) and chromium(III) challenge may indicate that exposure to both compounds may induce sensitivity or that there is cross-sensitivity between chromium(VI) and chromium(III) compounds on challenge. Similar results have been reported with high-dose chromium(III), showing that patch testing of chromium(VI)-sensitive patients with chromium(III) compounds can elicit an allergic reaction (Fregert and Rorsman 1964, 1966; Mali et al. 1966).

A study was performed on 54 volunteers who with chromium-induced allergic contact dermatitis to determine a dose-response relationship and to determine a minimum-elicitation threshold concentration (MET) that produces an allergic response in sensitive individuals (Nethercott et al. 1994). Patch testing was performed on the subjects in which the concentration of potassium chromate(VI) was varied up to 4.4 $\mu\text{g}/\text{cm}^2$. Two percent (1/54) had a MET of 0.018. About 10% were sensitized at 0.089 $\mu\text{g}/\text{cm}^2$ and all were sensitized at 4.4 $\mu\text{g}/\text{cm}^2$. Comparable studies were performed with chromium(III) chloride, however, only 1 showed a positive response at 33 $\mu\text{g}/\text{cm}^2$, and upon retesting was negative. Based on these findings the authors concluded that soil concentrations of chromium(VI) and chromium(III) of 450 and 165,000 ppm, respectively, should not pose a hazard of allergic contact dermatitis to 99.99% of people who might be exposed to chromium through soil-skin contact.

Subjects with a sensitivity to chromium and challenged with a 0.001% solution potassium dichromate had increased skin thickness and blood flow (Eun and Marks 1990). Studies conducted on chromium(VI)-

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sensitive printers and lithographers indicate that chromium(VI) compounds elicit reactions more frequently than do chromium(III) compounds (Levin et al. 1959; Mali et al. 1966; Samitz and Shrager 1966). The authors attributed this to a greater degree of permeation of the hexavalent form than the trivalent form through the skin (see Section 3.4.1.3).

In a study of skin disease among workers at an automobile factory, 230 workers with skin disease and 66 controls were patch tested with potassium dichromate (0.175% chromium(VI)). Sensitivity to potassium dichromate was seen in 24% of the patients and 1% of the controls. Most of the sensitive patients were assemblers who handled nuts, bolts, screws, and washers, which were found to have chromate on the surfaces as a result of a chromate dip used in the engine assembly process. Discontinuation of use of the chromate dip resulted in a significant decrease in the prevalence of dermatitis 6 months later (Newhouse 1963).

Numerous studies have investigated the cause of dermatitis in patients and in workers in a variety of occupations and industries and have found positive results for chromium compounds in patch tests. In these studies, patch tests were conducted with chromium(VI) or chromium(III) compounds using various concentrations. In studies of individuals with occupational contact dermatosis, positive patch tests for chromium (potassium dichromate, sodium chromate, or otherwise not specified) were found in 6–45% of the subjects (Athavale et al. 2007; Bock et al. 2003; Fregert 1975). The common occupations of individuals with the positive reactions to chromium were metal workers, tannery workers, builders, bricklayers, concrete workers, plasterers, and construction workers. Other industries and sources of chromium that have resulted in chromium sensitivity include welding, printing, glues, wood ash, foundry sand, match heads, machine oils, timber preservative, boiler linings, making of television screens, magnetic tapes, tire fitting, chrome plating, wood and paper industry, leather tanning, cement working, automobile painting, diesel locomotive repair, and milk testing (Burrows 1983; Cheng et al. 2008; Engebrigtsen 1952; Engel and Calnan 1963; Gass and Todd 2007; Kaplan and Zeligman 1962; Lockman 2002; Peltonen and Fraki 1983; Wong et al. 1998). Chromate sensitivity has also been reported in women who frequently used dichromate-containing detergent and bleach (Basketter et al. 2001; Wahba and Cohen 1979).

A number of large-scale retrospective studies (>3,000 subjects) examined the frequency of positive patch tests for potassium dichromate among patients with suspected contact dermatitis. Positive results were found in 2.7–6% of the subjects (Carøe et al. 2010; Cheng et al. 2008; Ertam et al. 2008; Hegewald et al. 2008). A similar frequency of positive patch test results were found in a study of elderly patients (11%)

with contact and occupational dermatosis (Balato et al. 2008) and in children (7%) with contact dermatitis (Milingou et al. 2010).

Animals can also be sensitized to chromium compounds. Contact sensitivity was induced in mice by rubbing a solution of 1% potassium dichromate (0.35% chromium(VI)) \approx 50 times on the shaved abdomens. Challenge with potassium dichromate on the ear resulted in significant induction of sensitivity, measured by ear thickness and histologically observed infiltration of nucleophilic leukocytes (Mor et al. 1988).

Guinea pigs can be sensitized to chromium(VI) and chromium(III) compounds by a series of intradermal injections of 0.009 mg chromium(VI)/kg as potassium dichromate or of 0.004 mg chromium(III)/kg as chromium trichloride. Regardless of the compound used to sensitize the guinea pigs, subsequent patch testing with chromium(VI) or chromium(III) yielded the same erythmatic reaction. The response, however, was greater when chromium(VI) was used as the sensitizer (Gross et al. 1968). Similarly, the same erythmatic response to chromium(VI) and chromium(III) compounds was noted in guinea pigs sensitized to 0.04 mg chromium(VI)/kg as potassium dichromate or 0.03 mg chromium(III)/kg as chromium sulfate (Jansen and Berrens 1968).

Results of skin testing to demonstrate or diagnose chromium sensitization are recorded in [Table 3-6](#) for chromium(VI) and [Table 3-7](#) for chromium(III).

No studies were located regarding the following health effects in humans or animals after dermal exposure to chromium compounds:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to chromium compounds.

3.3 GENOTOXICITY

In vivo studies of chromium compounds are summarized in Table 3-8. *In vitro* studies on the genotoxicity of chromium(VI) and chromium(III) compounds are summarized in Tables 3-9 and 3-10, respectively. Chromium(VI) compounds rapidly (within seconds to minutes) enter cells by facilitated diffusion, while chromium(III) compounds enter much more slowly (within days) by simple diffusion; therefore, chromium(VI) compounds are of greater concern with regard to health effects. Available genotoxicity studies on occupationally exposed humans typically evaluate effects in blood cells since blood is easily accessible, whereas evaluation of effects in cells from cancer target tissues (e.g., lung, gastrointestinal tract) are not easily obtained for analysis. However, negative genotoxicity results in tissues that are not cancer targets (e.g., blood) should not be extrapolated to cancer target tissues.

Occupational exposure studies have yielded mixed results on the genotoxic potential of chromium compounds. Studies involving workers exposed to chromium(VI) in stainless steel welding and electroplating (Halasova et al. 2008; Husgafvel-Pursiainen et al. 1982; Littorin et al. 1983; Nagaya 1986; Nagaya et al. 1991), and to chromium(III) in tanneries (Hamamy et al. 1987) did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers. No elevations in DNA strand breaks or hydroxylation of deoxyguanosine were detected in lymphocytes of workers exposed to chromium(VI) involved in the production of bichromate (Gao et al. 1994), while DNA strand breaks were reported in the peripheral lymphocytes of 19 chromium platers (Gambelunghie et al. 2003). DNA damage was also reported in chromium(III) tannery workers (Zhang et al. 2008). In contrast, other studies involving electroplaters, stainless steel welders, or workers at tanneries reported higher levels of chromosomal aberrations, sister chromatid exchanges, or micronuclei formation in workers exposed to chromium(VI) compared to controls (Balachandar et al. 2010; Deng et al. 1988; Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982; Werfel et al. 1998).

Urine samples from six workers working in chromium plating factories were tested for the induction of unscheduled DNA synthesis (UDS) in pleural mesothelial cells (Pilliere et al. 1992). The mean chromium concentration in the urine samples was 11.7 ± 8.8 $\mu\text{g/L}$. The urine from five of the workers showed a significant elevated in UDS over control subjects who were nonsmokers, with a trend toward increasing amounts of urine being tested. However, there was no correlation between UDS and chromium concentrations in urine.

Table 3-8. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
<i>Drosophila melanogaster</i>	Gene mutation	+	Gava et al. 1989b; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Zimmering et al. 1985	(VI)	Potassium dichromate, sodium dichromate, chromium trioxide, calcium chromate
<i>D. melanogaster</i>	Gene mutation	+	Olvera et al. 1993	(VI)	Chromium trioxide
<i>D. melanogaster</i>	Gene mutation	+	Kaya et al. 2002	(VI)	Potassium dichromate
<i>D. melanogaster</i>	Gene mutation	+	Amrani et al. 1999	(VI)	Potassium chromate, potassium dichromate
<i>D. melanogaster</i>	Gene mutation	–	Amrani et al. 1999	(III)	Chromium chloride
Human lymphocytes	Chromosomal aberrations	+	Koshi et al. 1984; Sarto et al. 1982	(VI)	Stainless steel, welding fumes, chromium trioxide
Human lymphocytes	Chromosomal aberrations	–	Hamamy et al. 1987	(III)	Chrome alum (primarily chromium sulfate)
Human lymphocytes	Chromosomal aberrations	–	Husgafvel- Pursiainen et al. 1982	(VI)	Stainless steel, welding fumes
Human lymphocytes	Sister chromatid exchanges	+	Koshi et al. 1984; Lai et al. 1998; Sarto et al. 1982; Stella et al. 1982	(VI)	Chromium plating, stainless steel, welding fumes, chromium trioxide
Human lymphocytes	DNA strand breaks, hydroxylation of deoxyquanosine	–	Gao et al. 1994	(VI)	Production of bichromate
Human lymphocytes	Sister chromatid exchanges	–	Nagaya et al. 1991	(VI)	Chromium plating
Human lymphocytes	Sister chromatid exchanges, DNA strand breaks	+	Werfel et al. 1998	(VI)	Welding fumes

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Table 3-8. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Human peripheral lymphocytes	Chromosomal aberrations	–	Halasova et al. 2008	(VI)	Welding fumes
Human lymphocytes	Sister chromatid exchanges	–	Nagaya 1986	(VI)	Chromium plating
Human peripheral lymphocytes	Micronuclei	+	Vaglenov et al. 1999	(VI)	Chromium electroplating
Human peripheral lymphocytes	Micronuclei	+	Benova et al. 2002	(VI)	Chromium plating
Human buccal mucosa	Micronuclei	+	Benova et al. 2002	(VI)	Chromium plating
Human peripheral lymphocytes	Chromosomal aberrations, sister chromatid exchanges	–	Benova et al. 2002	(VI)	Chromium plating
Human peripheral lymphocytes	DNA strand breaks	+	Gambelunghe et al. 2003	(VI)	Chromium plating
Human buccal mucosa	Chromosomal aberrations, sister chromatid exchanges	–	Benova et al. 2002	(VI)	Chromium plating
Human whole blood cells	Sister chromatid exchanges	+	Wu et al. 2001	(VI)	Chromium electroplating
Human peripheral lymphocytes	Micronuclei, DNA-protein crosslinks	+	Medeiros et al. 2003a	(III)	Tanners
Human peripheral lymphocytes	Chromosomal aberrations, micronuclei	+	Balachandar et al. 2010	(VI)	Tanners
Human peripheral lymphocytes	Micronuclei	–	Medeiros et al. 2003a	(VI)	Welders
Human peripheral lymphocytes	DNA-protein crosslinks	+	Medeiros et al. 2003a	(VI)	Welders
Human peripheral lymphocytes	DNA damage	+	Zhang et al. 2008	(III)	Tanners
Human peripheral lymphocytes	DNA damage	+	Zhang et al. 2011	(VI)	Chromium electroplating
New polychromatic erythrocytes	Micronuclei	+	LeCurieux et al. 1992	(VI)	Potassium chromate
Rat lung (intratracheal exposure)	DNA alterations	+	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (intratracheal exposure)	DNA alterations	–	Izzotti et al. 1998	(VI)	Sodium dichromate
Rat liver (oral exposure)	DNA-protein crosslinks	+	Coogan et al. 1991a	(VI)	Potassium chromate

Table 3-8. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Rat liver and kidney nuclei (intraperitoneal exposure)	DNA crosslinks, DNA-protein crosslinks, DNA strand breaks	–	Cupo and Wetterhahn 1985	(III)	Chromium oxide
Rat liver, kidney, and lung nuclei (intraperitoneal exposure)	DNA-protein crosslinks	+	Tsapalos et al. 1983b	(VI)	Sodium dichromate
Rat hepatocytes (oral exposure)	Unscheduled DNA synthesis	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Rat (F344/N) bone marrow cells (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate
Rat (Sprague-Dawley) hepatic	DNA fragmentation	–	Shara et al. 2005	(III)	Niacin-bound chromium
Mouse erythrocytes (oral exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse (B ₆ C ₃ F ₁ , BALB/c) erythrocytes (oral exposure)	Micronuclei	–	NTP 2007	(VI)	Sodium dichromate dihydrate
Mouse (am3-C57BL/6) erythrocytes (oral exposure)	Micronuclei	+	NTP 2007	(VI)	Sodium dichromate dihydrate
Mouse B ₆ C ₃ F ₁ (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate monohydrate
Mouse (B ₆ C ₃ F ₁) erythrocytes (oral exposure)	Micronuclei	–	NTP 2008b	(III)	Chromium picolinate monohydrate
Mouse (transplacental exposure)	DNA deletions	+	Kirpnick-Sobol et al. 2006	(III)	Chromium (III) chloride salt
Mouse (transplacental exposure)	DNA deletions	+	Kirpnick-Sobol et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	–	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate

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Table 3-8. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (BDF1) peripheral blood cells (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(III)	Chromic potassium sulfate dodecahydrate
Mouse (BDF1) bone marrow cells (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(III)	Chromic potassium sulfate dodecahydrate
Mouse (BDF1) bone marrow cells (gavage exposure)	Micronuclei	—	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (BDF1) bone marrow cells (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) bone marrow—dams (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) bone marrow—dams (drinking water exposure)	Micronuclei	—	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) bone marrow—dams (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) bone marrow—dams (intraperitoneal exposure)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal liver cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal liver cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from drinking water)	Micronuclei	—	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate

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Table 3-8. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from drinking water)	Micronuclei	–	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal liver cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal liver cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Sodium dichromate dihydrate
Mouse (Swiss) fetal peripheral blood cells (transplacental exposure from intraperitoneal injection)	Micronuclei	+	De Flora et al. 2006	(VI)	Potassium dichromate
Mouse leukocytes	DNA damage	+	Devi et al. 2001	(VI)	Potassium dichromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Shindo et al. 1989	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1997; Wild 1978	(VI)	Potassium chromate
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	–	Itoh and Shimada 1996	(III)	Chromium chloride
Mouse erythrocytes (intraperitoneal exposure)	Micronuclei	+	Itoh and Shimada 1996	(VI)	Potassium chromate
Mouse peripheral lymphocytes	DNA damage	+	Wang et al. 2006	(VI)	Potassium chromate
Mouse bone marrow cells (oral exposure)	Micronuclei	–	Mirsalis et al. 1996	(VI)	Potassium chromate
Mouse bone marrow cells (gavage)	Chromosomal aberrations	+	Sarkar et al. 1993	(VI)	Chromium trioxide
Mouse bone marrow (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1998	(VI)	Potassium dichromate
Mouse hepatocytes (intraperitoneal exposed)	Cell mutation	+	Itoh and Shimada 1997, 1998	(VI)	Potassium dichromate

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Table 3-8. Genotoxicity of Chromium *In Vivo*

Species (test system)	End point	Results	Reference	Valence	Compound
Mouse bone marrow (intraperitoneal exposed)	Micronuclei	+	Chorvatovičová et al. 1993; Wrońska-Nofer et al. 1999	(VI)	Potassium dichromate
Mouse (intraperitoneal exposure)	Dominant lethality	+	Paschin et al. 1982	(VI)	Potassium dichromate
Mouse liver and kidney cells (intraperitoneal exposure)	Single strand breaks	+	Ueno et al. 2001	(VI)	Potassium dichromate
Mouse spleen, lung, and brain cells (intraperitoneal exposure)	Single strand breaks	–	Ueno et al. 2001	(VI)	Potassium dichromate

– = negative results; + = positive results; (0) = 0 valence; (III) = trivalent; (VI) = hexavalent; DNA = deoxyribonucleic acid

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Table 3-9. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Subcellular targets:					
<i>Escherichia coli</i> DNA	DNA-protein crosslinks	No data	–	Fornance et al. 1981	Potassium chromate
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	–	Fornance et al. 1981	Potassium chromate
Double-stranded M13mp2 bacteriophage DNA transferred to <i>E. coli</i>	Forward mutations	No data	+	Snow and Xu 1989	Potassium chromate
Puc 19 plasmid DNA	Gene mutation	No data	+	Kortenkamp et al. 1996b	Potassium chromate
Papilloma virus	Gene mutation	No data	+	Kowalski et al. 1996	Potassium chromate
PSV2neo-based plasmid DNA	DNA polymerase arrest	+	–	Bridgewater et al. 1994b, 1998	Sodium dichromate
Prokaryotic organisms:					
<i>Bacillus subtilis</i>	Recombinations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1975	Potassium chromate, potassium dichromate
<i>E. coli</i> PQ37, PQ35	Induction of SOS response	–	+	Olivier and Marzin 1987	Potassium chromate, potassium dichromate
<i>E. coli</i> AB1157, GC2375, UA4202, PQ30	Induction of SOS response	No data	+	Llagostera et al. 1986	Chromium chromate, potassium dichromate, chromium trioxide
<i>E. coli</i> Wp2, Hs30R, B/rWP2	Reverse mutations	No data	+	Kanematsu et al. 1980; Nakamuro et al. 1978; Venitt and Levy 1974	Potassium dichromate, potassium chromate, sodium chromate

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Table 3-9. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>E. coli</i> , WP2/pKM101, WP2 uvrA/pKM101	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
<i>E. coli</i> , WP2 uvrA/pKM101	Reverse mutations	+	+	NTP 2007	Sodium dichromate dihydrate
<i>Salmonella typhimurium</i> TA100, TA98	Reverse mutations	+	+	NTP 2007	Sodium dichromate dihydrate
<i>S. typhimurium</i> TA100	Base pair substitutions	No data	+	DeFlora 1978	Sodium dichromate
<i>S. typhimurium</i> TA100	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA102	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA92	Base pair substitutions	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1535	Base pair substitutions	No data	—	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA97	Frame shift mutations	No data	+	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1537, TA1538	Frame shift mutations	No data	—	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1978	Frame shift mutations	No data	±	Bennicelli et al. 1983	Sodium dichromate
<i>S. typhimurium</i> TA1535	Base pair substitutions	—	±	Nakamura et al. 1987	Potassium dichromate
<i>S. typhimurium</i> TA100	Base pair substitutions	+	+	Venier et al. 1982	Potassium dichromate
<i>S. typhimurium</i> TA1538	Frame shift mutations	—	—	Venier et al. 1982	Potassium dichromate
<i>S. typhimurium</i> TA98	Frame shift mutations	—	±	Venier et al. 1982	Potassium dichromate
<i>S. typhimurium</i> TA97a, TA98	Frame shift mutations	+	+	Tagliari et al. 2004	Potassium dichromate
<i>S. typhimurium</i> TA100, TA102	Base pair substitutions	+	+	Tagliari et al. 2004	Potassium dichromate

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Table 3-9. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>S. typhimurium</i> TA100	Base pair substitutions	–	–	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
<i>S. typhimurium</i> TA1535	Base pair substitutions	No data	+	DeFlora 1981	Sodium dichromate, potassium chromate, calcium chromate, ammonium chromate, chromium trioxide
<i>S. typhimurium</i> TA100, TA1535	Base pair substitutions	No data	+	Haworth et al. 1983	Calcium chromate
<i>S. typhimurium</i> TA98, TA1537	Frame shift mutations	No data	+	Haworth et al. 1983	Calcium chromate
<i>S. typhimurium</i> TA100, TA1535	Base pair substitutions	No data	–	Kanematsu et al. 1980	Potassium dichromate
<i>S. typhimurium</i> TA100, TA1537, TA1538	Frame shift mutations	No data	–	Kanematsu et al. 1980	Potassium dichromate
<i>S. typhimurium</i> TA 1535 pSK1002	Mutations	+	+	Yamamoto et al. 2002	Potassium dichromate
<i>S. typhimurium</i> TA102, TA2638	Reverse mutations	No data	+	Watanabe et al. 1998a	Chromium trioxide, sodium dichromate
Eukaryotic organisms:					
Yeasts:					
<i>Saccharomyces cerevisiae</i> D7	Mitotic gene conversions	No data	+	Fukunaga et al. 1982; Singh 1983	Chromium trioxide
<i>S. cerevisiae</i> D7	Reverse mutations	No data	+	Singh 1983	Potassium dichromate
<i>S. cerevisiae</i> D7	Mitotic cross-over	No data	+	Fukunaga et al. 1982	Chromium trioxide
<i>S. cerevisiae</i>	DNA deletions	No data	+	Kirpnick-Sobol et al. 2006	Potassium dichromate

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Table 3-9. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>Schizosacharomyces pombe</i>	Mitotic gene conversion	No data	+	Bonatti et al. 1976	Potassium dichromate
<i>S. pombe</i>	Forward mutations	No data	+	Bonatti et al. 1976	Potassium dichromate
Chickens:					
Chick embryos	DNA damage cross links, strand breaks, DNA-protein crosslinks	No data	+	Tsapakos et al. 1983a	Sodium chromate
Mammalian cells:					
Human embryonic lung fibroblasts (IMR-90)	DNA-protein crosslinks, DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human bronchial epithelial cells	DNA fragmentation	No data	+	Fornance et al. 1981	Potassium chromate
Human lymphocytes	Single strand breaks	No data	+	Depault et al. 2006	Potassium chromate
Human lymphocytes	DNA damage	No data	+	Blasiak and Kowalik 2000	Potassium dichromate
Human dermal fibroblasts (GM03440 cells)	DNA double-strand breaks	No data	+	Ha et al, 2003, 2004	Sodium chromate
Human bronchial fibroblasts (WTHBF-6 cells)	chromosome aberrations	No data	+	Holmes et al. 2006	Sodium chromate
Human bronchial fibroblasts (WTHBF-6 cells)	Disruption of mitosis	No data	+	Wise et al. 2006a	Sodium chromate
Human bronchial epithelial cells (BEP2D cells)	chromosome aberrations	No data	+	Wise et al. 2006b	Sodium chromate
Human lung fibroblasts	DNA polymerase arrest, DNA-DNA crosslinks	No data	+	Xu et al. 1996	Sodium chromate
Primary human bronchial fibroblasts	Chromosomal aberrations	No data	+	Li Chen et al. 2009	Sodium chromate
Primary human skin cells	Chromosomal aberrations	No data	+	Li Chen et al. 2012	Sodium chromate

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Table 3-9. Genotoxicity of Chromium(VI) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Chinese hamster lung DON cells	Sister chromatid exchange, chromosomal aberrations	No data	+	Koshi 1979, Koshi and Iwaski 1983	chromium trioxide, zinc bromate, calcium chromate, potassium chromate
Chinese hamster ovary cells	Chromosomal aberrations, DNA fragmentation	No data	+	Blankenship et al. 1997	sodium chromate
Mouse L1210 leukemia cells	DNA fragmentation, DNA-protein crosslinks	No data	+	Fornace et al. 1981	Potassium chromate
Mouse embryo fibroblast cells	Chromosomal aberrations	No data	+	Sugiyama et al. 1986a	Calcium chromate
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	+	Raffetto et al. 1977	Potassium dichromate
Mouse primary fetal cells	Transformations, chromosomal aberrations	No data	+	Raffetto et al. 1977	Potassium dichromate
Human gastric mucosa	DNA damage	No data	+	Trzeciak et al. 2000	Potassium dichromate
Human peripheral blood lymphocytes	DNA damage	No data	+	Trzeciak et al. 2000	Potassium dichromate
Human fibroblasts	Double strand breaks	No data	+	Ha et al. 2004	Sodium chromate
Human primary bronchial fibroblasts	Chromosomal aberrations	No data	+	Wise et al. 2002, 2004	Sodium chromate
Chinese hamster ovary cells	Chromosomal damage	No data	+	Seoane and Dulout 1999	Potassium dichromate
Mouse mammary FM3A carcinoma cells	Chromosomal aberrations	No data	+	Umeda and Nishmura 1979	Potassium dichromate, potassium chromate, chromium trioxide
Rat liver epithelial cells	Transformations	No data	+	Briggs and Briggs 1988	Potassium chromate

- = negative results; + = positive results; ± = weakly positive results; (VI) = hexavalent; DNA = deoxyribonucleic acid

Table 3-10. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Subcellular targets:					
<i>Escherichia coli</i> DNA	DNA-protein crosslinks	No data	+	Fornace et al. 1981	Chromium trichloride
Nuclei of mouse L1210 leukemia cells	DNA fragmentation	No data	+	Fornace et al. 1981	Chromium trichloride
Single-stranded M13mp2 bacteriophage DNA	Replication assay: increased nucleotide incorporation	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
Double-stranded M13mp2 bacteriophage DNA transferred to <i>E. coli</i>	Forward mutations	No data	+	Snow 1991; Snow and Xu 1989	Chromium trichloride
pSV2neoTS DNA	DNA polymerase arrest	No data	+	Bridgewater et al. 1994b	Chromium trichloride
Prokaryotic organisms:					
<i>Bacillus subtilis</i>	Recombinations	No data	—	Kanematsu et al. 1980	Chromium sulfate, chromium potassium sulfate
<i>B. subtilis</i>	Recombinations	No data	—	Matsui 1980; Nakamuro et al. 1978; Nishioka 1975	Chromium trichloride
<i>B. subtilis</i>	Recombinations	No data	±	Nakamuro et al. 1978	Chromium nitrate
<i>B. subtilis</i>	Recombinations	No data	±	Nakamuro et al. 1978	Chromium acetate
<i>E. coli</i>	Gene mutations	No data	+	Sugden et al. 1990	cis-Dichlorobis (2,2'-bipyridyl) chromium(III)
<i>E. coli</i> WP2 <i>uvrA</i> /pKM101	Gene mutations	—	—	NTP 2008b	Chromium picolinate monohydrate
<i>E. coli</i> AB1157, GC275, VA4202, PQ30	Induction of SOS response	No data	—	Llagostera et al. 1986	Chromium trichloride, chromium nitrate, chromium acetate
<i>E. coli</i> PQ37, PQ35	Induction of SOS response	—	—	Olivier and Marzin 1987	Chromium trichloride hexahydrate

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Table 3-10. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>E. coli</i> PQ37	Induction of SOS response	–	–	Venier et al. 1989	Chromium trichloride, chromium nitrate
<i>E. coli</i> PQ37	Induction of SOS response	–	±	Venier et al. 1989	Chromium acetate
<i>Salmonella typhimurium</i> TA100, TA1535	Reverse mutations Base pair substitutions	–	–	De Flora 1981; Petrilli and De Flora 1978b	Chromium trichloride hexahydrate, chromium nitrite, monohydrate, chromium potassium sulfate, chromium acetate, neochromium, chromium alum, chromite
TA98, TA1537, TA1538	Frame shift mutations	–	–		
<i>S. typhimurium</i> TA102	Base pair substitutions	–	–	Bennicelli et al. 1983	Chromium nitrate
<i>S. typhimurium</i> TA100, TA1535	Base pair substitutions	–	–	Venier et al. 1982	Chromium chloride hexahydrate, chromium nitrate monohydrate
TA98, TA1538	Frame shift mutations	–	–		
<i>S. typhimurium</i> TA100, TA98	Reverse mutations	–	–	NTP 2008b	Chromium picolinate monohydrate
<i>S. typhimurium</i> TA102, TA104, TA100, TA1535, TA97, TA98	Reverse mutations	–	–	NTP 2008b	Chromium picolinate
<i>S. typhimurium</i> TA92, TA98, TA100	Reverse mutations	No data	+	Warren et al. 1981	Chromium complexes with 2,2'-bipyridine and 1,10-phenanthroline
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Whittaker et al. 2005	Chromium picolinate
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Whittaker et al. 2005	Chromium chloride
<i>S. typhimurium</i> TA1535, TA97a, TA98, TA100, TA102	Reverse mutations	–	–	Shara et al. 2005	Niacin-bound chromium

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Table 3-10. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
<i>S. typhimurium</i> TA 1535 pSK1002	Mutations	–	–	Yamamoto et al. 2002	Chromium nitrate
Eukaryotic organisms:					
Yeasts:					
<i>Saccharomyces cerevisiae</i>	Reverse mutations, mitotic gene conversions	No data	+	Bronzetti et al. 1986	Chromium trichloride
<i>S. cerevisiae</i>	DNA deletions	No data	+	Kirpnick-Sobol et al. 2006	Chromium (III) chloride salt
Chickens:					
Chick embryos	DNA damage (crosslinks, strand breaks)	No data	–	Tsapakos et al. 1983a	Chromium nitrate
Mammalian cells:					
Human lymphocytes	DNA damage	No data	+	Blasiak and Kowalik 2000	Chromium chloride
Human skin fibroblasts	Unscheduled DNA synthesis	No data	–	Whiting et al. 1979	Chromium trichloride
Human skin fibroblasts	DNA fragmentation	No data	–	Whiting et al. 1979	Chromium trichloride
Human leukocytes	Chromosomal aberrations	No data	±	Nakamuro et al. 1978	Chromium trichloride, chromium nitrate, chromium acetate
Human lymphocytes	Chromosomal aberrations	No data	±	Stella et al. 1982	Chromium trichloride hexahydrate
Human lymphocytes	Chromosomal aberrations	No data	–	Sarto et al. 1980	Chromium trichloride
Human lymphocytes	Sister chromatid exchange	No data	–	Stella et al. 1982	Chromium trichloride hexahydrate
Chinese hamster V79 cells	Chromosomal aberrations	No data	–	Newbold et al. 1979	Chromium acetate
Syrian hamster embryonal cells	Chromosomal aberrations	No data	–	Tsuda and Kato 1977	Chromium trichloride hexachloride, chromium sulfate tetrahydrate
Chinese hamster lung DON cells	Chromosomal aberrations	No data	–	Ohno et al. 1982	Chromium trichloride hexahydrate, chromium sulfate tetrahydrate

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Table 3-10. Genotoxicity of Chromium(III) *In Vitro*

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Chinese hamster ovary cells	aberrations		±	Levis and Majone 1979	Chromium trichloride hexachloride, chromium nitrate monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Levis and Majone 1979; MacRae et al. 1979; Venier et al. 1982	Chromium trichloride hexachloride, chromium nitrate, monohydrate, chromium potassium sulfate, chromium acetate
Chinese hamster ovary cells (<i>hprt</i> locus)	Mutations	No data	+	Coryell and Stearns 2006; Stearns et al. 2002	Chromium trispicolinate
Mouse L5178Y+/- lymphoma	Mutations	–	–	Shara et al. 2005	Niacin-bound chromium
Mouse L5178Y lymphoma	Mutations	+	+	Whittaker et al. 2005	Chromium picolinate
Mouse L5178Y lymphoma	Mutations	–	±	Whittaker et al. 2005	Chromium chloride
Mouse leukemia cells	Chromosomal aberrations	No data	–	Fornace et al. 1981	Chromium trichloride
Mouse mammary carcinoma	Chromosomal aberrations	No data	–	Umeda and Nishimura 1979	Chromium sulfate
Fm3A cells:					
Mouse fetal cells	Chromosomal aberrations	No data	±	Raffetto et al. 1977	Chromium trichloride
Mouse fetal cells	Morphological transformations	No data	+	Raffetto et al. 1977	Chromium trichloride
Mouse A18BcR cells	Unscheduled DNA synthesis	No data	–	Raffetto et al. 1977	Chromium trichloride

– = negative results; + = positive results; ± = weakly positive results; (III) = trivalent; DNA = deoxyribonucleic acid

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An epidemiology study of stainless steel welders, with mean exposure levels of 0.055 mg chromium(VI)/m³ or 0.081 mg chromium (total)/m³, did not report increases in the number of sister chromatid exchanges in the lymphocytes of exposed workers. The welders were also exposed to nickel and molybdenum from the welding rods (Littorin et al. 1983). A similar study was conducted to detect genotoxic effects of chromium(VI) on workers in electroplating factories. Of the 24 workers examined, none showed significant differences in sister chromatid exchange frequency (Nagaya 1986). Similarly, no correlation was found between excretion of chromium in the urine and the frequency of sister chromatid exchanges in 12 male chromium platers whose mean urinary chromium level was 17.9 µg/g creatinine (Nagaya et al. 1991). In chrome platers (n=15) in low (0.0075 mg Cr(VI)/m³) and high (0.0249 mg Cr(VI)/m³) exposure groups, no significant differences in the frequency of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes and buccal mucosa cells were observed compared to controls (0.0004 mg Cr(VI)/m³; n=15) (Benova et al. 2002). No increase in chromosomal aberrations was observed in 17 tannery workers exposed primarily to chromium(III) as compared with 13 controls (Hamamy et al. 1987). However, parallel measurements in these tannery workers showed that the average chromium levels in plasma (0.115 µg/L) and urine (0.14 µg/100 L) did not differ from the nonexposed workers. In addition, stainless steel welders occupationally exposed to chromium(VI) for a mean of 21 years did not have any increase in chromosomal aberrations or sister chromatid exchanges compared to a control group; no actual exposure levels were provided (Husgafvel-Pursiainen et al. 1982). Similarly, no alterations in chromosomal aberration frequency were observed in chromium welders exposed to chromium for an average of 10 years (Halasova et al. 2008). Yet, other studies involving electroplaters and welders report a higher incidence of chromosomal aberrations or sister chromatid exchanges in lymphocytes of workers than in controls. In one study, a causal relationship between chromium exposure and the observed effects could not be established because the exposure was confounded by co-exposure to nickel and manganese (Elias et al. 1989a). In another study, although chromium workers were found to have higher rates of sister chromatid exchanges than workers exposed to nickel-chromium or controls (after adjusting for potential confounding factors), the differences were not significantly correlated to chromium concentrations in blood or urine (Lai et al. 1998). The frequency of sister chromatid exchanges was also higher in the blood of 35 chromium platers in Taiwan when compared to controls (Wu et al. 2001). The frequency of sister chromatid exchanges in the lymphocytes of 12 workers exposed to chromium(VI) as chromic acid fumes in a chrome plating industry was significantly increased (Stella et al. 1982). Significantly increased incidences of chromosomal aberrations in peripheral lymphocytes were found in workers exposed to chromium(VI) as chromium trioxide in two of four electroplating plants. Of the two plants where the increases were significant, one was a "bright" plating plant, where exposure involved nickel as well as chromium, and one was a "hard"

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plating plant, where exposure involved only chromium. However, the increase in chromosomal aberrations correlated poorly with urinary chromium levels, and only the increase in the "bright" platers showed a significant correlation with duration of exposure. A significantly increased incidence of sister chromatid exchanges was found in "hard" platers compared with controls (sister chromatid exchange was not evaluated in "bright" platers), and smoking appeared to enhance the increase (7 of 8 smokers and 7 of 11 nonsmokers had incidences significantly higher than controls). Moreover, the increased incidence of sister chromatid exchange showed a positive correlation with urinary chromium levels (Sarto et al. 1982). Repeated cytogenetic analysis of peripheral lymphocytes for 3 years revealed an increased frequency of chromosomal aberrations and sister chromatid exchanges in a group of stainless steel welders compared to controls. The workers were exposed to unreported chromium(VI) concentrations for a mean of 12.1 years, but exposure to ultraviolet rays and small amounts of manganese, nickel, iron, and magnesium could not be ruled out (Koshi et al. 1984). Compared to 39 controls, significantly elevated sister chromatid exchange values in lymphocytes and significantly higher rates of DNA single-strand breakages were found in a group of 39 welders exposed to unreported chromium(VI) and nickel concentrations (Werfel et al. 1998). Only one study was located regarding the average levels of exposure for electroplating workers: workers exposed to an average level of 0.008 mg chromium(VI)/m³ had increases in chromosomal aberrations and sister chromatid exchanges. However, high levels of nickel as well as chromium were found in hair and stool samples when compared to controls (Deng et al. 1988). Increased levels of chromosomal aberrations and micronuclei formation were observed in tannery workers and residents living near the tannery exposed to elevated levels of chromium(VI) (Balachandar et al. 2010); chromium(VI) levels in air samples were 0.021 and 0.013 mg/m³ in the workers and residents, respectively, and 0.006 mg/m³ in controls. Increased frequencies of micronuclei were reported in the peripheral lymphocytes and buccal mucosa cells in two studies of chromium electroplating workers in Bulgaria (Benova et al. 2002; Vaglenov et al. 1999). In chrome platers (n=15), significant increases in micronuclei in peripheral lymphocytes and buccal mucosa cells were observed in low (0.0075 mg Cr(VI)/m³) and high (0.0249 mg Cr(VI)/m³) exposure groups compared to controls (0.0004 mg Cr(VI)/m³; n=15) (Benova et al. 2002). Increased micronuclei frequency and DNA-protein crosslinks were observed in the peripheral lymphocytes of tanners primarily exposed to chromium(III) compounds, while welders, who are primarily exposed to chromium(VI) compounds had evidence of DNA-protein crosslinks, but not increased micronuclei frequency in peripheral lymphocytes (Medeiros et al. 2003a). No elevated levels of DNA strand breaks or hydroxylation of deoxyguanosine in lymphocytes were found in 10 workers occupationally exposed in the production of bichromate when compared with 10 non-occupationally-exposed workers at the same facility (Gao et al. 1994). From general background monitoring levels of chromium(VI), exposures were estimated to be between 0.001 and 0.055 mg/m³. In

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contrast, DNA strand breaks were reported in the peripheral lymphocytes of 19 chromium platers with a mean postshift urinary concentration of 7.31 $\mu\text{g/g}$ creatinine when compared to non-exposed control subjects (Gambelunghe et al. 2003). Increases in DNA damage were found in tannery workers exposed to chromium(III) (Zhang et al. 2008). Significant associations between DNA damage and blood and urinary chromium levels were observed; blood chromium levels ranged from 13.10 to 68.30 $\mu\text{g/L}$ (median of 22.95 $\mu\text{g/L}$) and urinary chromium levels ranged from 1.50 to 42.20 $\mu\text{g/L}$ (median of 10.60 $\mu\text{g/L}$) in the high-exposure group and 4.30–64.3 $\mu\text{g/L}$ (median of 22.95 $\mu\text{g/L}$) and 1.50–18.00 $\mu\text{g/L}$ (median of 2.25 $\mu\text{g/L}$), respectively, in the low-exposure group. Increases in DNA damage were also found in electroplating workers exposed to chromium(VI) for an average of 5.3 years; significant associations between erythrocyte chromium levels and DNA damage were also observed (Zhang et al. 2011). Li et al. (2008) reported a significant correlation between umbilical cord chromium levels in neonates born to mothers living in a chromium-contaminated area of China (median umbilical cord chromium levels were 5 times higher than controls) and DNA damage.

Chromium(VI) and chromium(III) have been shown to be genotoxic in human cell lines. S phase-dependent DNA double-strand breaks were observed in cultured human dermal fibroblasts exposed to sodium chromate (chromium(VI)) (Ha et al. 2003, 2004). Sodium chromate also induced concentration-dependent chromosome damage in cultured human bronchial fibroblasts and bronchial epithelial cells (Holmes et al. 2006; Wise et al. 2006b). Exposure of cultured human bronchial fibroblasts to sodium chromate produced disruption of mitosis, most likely through spindle assembly checkpoint bypass (Wise et al. 2006a). Weakly positive responses were observed for chromium(III) (Nakamuro et al. 1978; Stella et al. 1982). However, it should be noted that in positive studies, the genotoxic potency of chromium(III) compounds was several orders lower than that of chromium(VI) compounds tested in the same systems. Positive results for increased micronuclei and DNA damage were also observed in lymphocytes exposed to chromium(III) chloride (Blasiak and Kowalik 2000). Positive results of chromium(III) in intact cells could be due to contamination of the test compounds with traces of chromium(VI) (De Flora et al. 1990; IARC 1990), nonspecific effects at very high doses, experimental conditions that would increase the penetration of chromium(III) into cells (e.g., detergents), or a technical artifact formed during the extraction procedures (De Flora et al. 1990). In one case, chromium(III) compounds showed genotoxicity that was linked to redox cycling of a chromium-DNA complex (Sugden et al. 1990). Although chromium(III) compounds are less toxic than chromium(VI) compounds because of its relative inability to cross cell membranes, chromium(III) causes more DNA damage and mutations when it is formed by intracellular reduction from chromium(VI) or it is reacted with DNA in subcellular systems (Bridgewater et al. 1994a, 1994b, 1998; Fornace et al. 1981; Snow 1991; Snow and Xu 1989).

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Thus, results of studies in occupationally exposed humans and in human cell lines indicate that chromium(VI) and chromium(III) are genotoxic; however, studies in humans were limited in several aspects. Generally, the levels of exposure to chromium(VI) were not known and co-exposure to other potentially active compounds (namely ultraviolet rays and other potentially genotoxic metals) occurred in several studies. Some negative results (Hamamy et al. 1987) were probably due to low exposure, because the chromium levels in plasma and urine of exposed and unexposed workers did not differ. Furthermore, some of the studies (Deng et al. 1988; Hamamy et al. 1987; Stella et al. 1982) used groups that were too small (<20 individuals) to have the statistical power to reliably assess the cytogenetic changes in workers. Although most older occupational exposure studies gave negative or equivocal results, most recent studies have identified chromosomal effects in exposed workers (Benova et al. 2002; Gambelunghe et al. 2003; Wu et al. 2001). Furthermore, results of studies in human cell lines provide evidence of the genotoxic activity of chromium compounds. Thus, the available studies support that chromium compounds, particularly chromium(VI), have carcinogenic potential because interactions with DNA have been linked with the mechanism of carcinogenicity. No studies were located regarding genotoxic effects in humans after oral exposure to chromium or its compounds.

Numerous studies have evaluated the genotoxicity of chromium compounds in animals by several exposure routes, including oral, inhalation, and parenteral routes. No increased incidence of micronuclei in polychromatic erythrocytes was observed in mice given single gavage doses of potassium chromate at ≤ 86 mg chromium(VI)/kg (Shindo et al. 1989) or in mice exposed to potassium chromate via drinking water at 1–20 ppm for 48 hours or to bolus doses up to 4 μ g/kg for 2 days (Mirsalis et al. 1996). Similarly, no UDS in hepatocytes was found in rats. However, an increase in DNA-protein crosslinking was found in the livers of rats exposed to potassium chromate in the drinking water at ≥ 6 mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a).

The clastogenic effects of male Swiss albino mice fed chromium(VI) trioxide (20 mg/kg body weight) by gavage were studied; after 24 hours, bone marrow cells were isolated and 500 metaphase plates were scored for chromosomal aberrations (Sarkar et al. 1993). The treated cells showed a significant increase in aberrations per cell over controls by 4.4-fold. When animals were treated simultaneously with chlorophyllin (1.5 mg/kg), a sodium-copper derivative of chlorophyll and an antioxidant, numbers of aberrations were reduced to nearly background levels.

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An increase in DNA-protein crosslinking was found in the livers of rats that had been exposed to potassium chromate in the drinking water at ≥ 6 mg chromium(VI)/kg/day for 3 or 6 weeks (Coogan et al. 1991a). Bone marrow cells from male mice fed chromium(VI) trioxide at 20 mg chromium(VI)/kg by gavage had a 4.4-fold increase in chromosomal aberration over controls (Sarkar et al. 1993). Significant DNA alterations were seen in the lung, but not the liver, of rats exposed to chromium(VI) by intratracheal instillation of sodium dichromate (Izzotti et al. 1998). DNA damage was also reported in leukocytes and peripheral lymphocytes of mice orally exposed to chromium(VI) as potassium chromate (Devi et al. 2001; Wang et al. 2006), and transplacental exposure of potassium dichromate resulted in DNA deletions of the retinal pigment epithelium of mice (Kirpnick-Sobol et al. 2006). Intraperitoneal exposure to chromium(VI) as potassium dichromate caused single strand breaks in mouse liver and kidney cells, but did not in spleen, lung, or brain cells (Ueno et al. 2001). Micronucleated polychromatic erythrocytes were found in mice following intraperitoneal exposure to chromium(VI) as potassium dichromate (Chorvatovičová et al. 1993; De Flora et al. 2006; Itoh and Shimada 1996, 1997; Wild 1978; Wrońska-Nofer et al. 1999), though one study reported negative results following intraperitoneal exposure to potassium chromate (Shindo et al. 1989). In contrast, oral exposure of mice to chromium(VI), as potassium dichromate or sodium dichromate dihydrate, did not induce micronuclei in bone marrow or in peripheral blood cells (De Flora et al. 2006; Mirsalis et al. 1996; NTP 2008a). Similar to chromium(VI) compounds, oral exposure of chromium(III) compounds also did not induce micronuclei in mouse erythrocytes (NTP 2008b), bone marrow cells (De Flora et al. 2006; NTP 2008b), or in peripheral blood cells (De Flora et al. 2006). Transplacental exposure to fetuses from dams exposed to chromium(VI) as either sodium dichromate dihydrate or potassium dichromate through drinking water did not result in micronuclei in fetal liver or peripheral blood cells (De Flora et al. 2006), while transplacental exposure to fetuses from dams exposed by intraperitoneal injection to these same chromium(VI) compounds did result in micronuclei in both fetal liver and peripheral blood cells (De Flora et al. 2006).

No unscheduled DNA synthesis was found in rat hepatocytes after the rats were exposed to potassium chromate in drinking water (Mirsalis et al. 1996). The contrasting results may relate to route-specific differences in absorption or metabolic fate of chromate *in vivo*. Furthermore, intraperitoneal exposure to chromium(VI) as potassium dichromate induced dominant lethality in mice (Paschin et al. 1982) and a significant increase in mutant frequency within mouse hepatocytes (Itoh and Shimada 1997, 1998) and bone marrow cells (Itoh and Shimada 1998). Intraperitoneal injection in rats with sodium dichromate chromium(VI) resulted in DNA crosslinks in liver, kidney, and lung nuclei (Tsapakos et al. 1983b), while similar injection in rats with chromium(III) trichloride did not cause DNA interstrand crosslinks, DNA-protein crosslinks, or DNA strand breaks in liver and kidney nuclei (Cupo and Wetterhahn 1985). Oral

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exposure to niacin-bound chromium(III) did not cause DNA fragmentation in rats after 90 days of dietary exposure at doses >621.6 mg Cr(III)/kg/day (Shara et al. 2005). In addition, studies in *Drosophila melanogaster* showed an induction of gene mutations after exposure to chromium(VI) (Amrani et al. 1999; Gava et al. 1989a; Kaya et al. 2002; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Olvera et al. 1993; Zimmering et al. 1985), but not after exposure to chromium(III) (Amrani et al. 1999).

The vast majority of studies reported genotoxic effects of chromium(VI) in mammalian cells *in vitro* (Blasiak and Kowalik 2000; Briggs and Briggs 1988; Depault et al. 2006; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Gomez-Arroyo et al. 1981; Ha et al. 2004; Koshi 1979; Koshi and Iwasaki 1983; Kowalski et al. 1996; Levis and Majone 1979; Li Cheng et al. 2008, 2011; MacRae et al. 1979; Majone and Levis 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Seoane and Dulout 1999; Stella et al. 1982; Sugiyama et al. 1986a; Trzeciak et al. 2000; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979; Wise et al. 2002, 2003; Yang et al. 1992). Chromium(VI) also induced DNA damage (DNA interstrand crosslinks, DNA strand breaks, DNA-protein crosslinks) in cultured chick embryo hepatocytes (Tsapakos et al. 1983a). In contrast, mostly negative results were reported for chromium(III) in mammalian cells (Fornace et al. 1981; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarto et al. 1980; Shara et al. 2005; Stella et al. 1982; Tsuda and Kato 1977; Umeda and Nishimura 1979; Venier et al. 1982; Whiting et al. 1979) and chick embryo hepatocytes (Tsapakos et al. 1983a). Positive results were obtained in Chinese hamster ovary cells (Coryell and Stearns 2006; Levis and Majone 1979; Stearns et al. 2002), mouse fetal cells (Raffetto et al. 1977), and mouse lymphoma cells (Whittaker et al. 2005). Chromium(III) picolinate caused chromosome damage (Stearns et al. 1995b) and mutations in cultured mammalian cells (Stearns et al. 2002).

Chromium(VI) was genotoxic in *Saccharomyces cerevisiae* (Fukunaga et al. 1982; Kirpnick-Sobol et al. 2006; Singh 1983) and *Schizosaccharomyces pombe* (Bonatti et al. 1976). Two studies demonstrated the genotoxicity of chromium(III) in *S. cerevisiae* (Bronzetti et al. 1986; Kirpnick-Sobol et al. 2006).

In vitro studies indicated that soluble chromium(VI) compounds are mutagenic in *Salmonella typhimurium* reverse mutation assays (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Nakamura et al. 1987; NTP 2007a; Venier et al. 1982; Watanabe et al. 1998a; Yamamoto et al. 2002), and in a *Salmonella* microsuspension bioassay (Tagliari et al. 2004). Only one study reported negative results with chromium(VI) in all tested strains (Kanematsu et al. 1980). In contrast, studies with chromium(III)

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did not report the induction of reverse mutations in *S. typhimurium* (Bennicelli et al. 1983; De Flora 1981; NTP 2008b; Petrilli and De Flora 1978b; Shara et al. 2005; Venier et al. 1982; Whittaker et al. 2005; Yamamoto et al. 2002). After preincubation with mammalian microsomes, the mutagenicity of chromium(VI) compounds was reduced or abolished due to concentrations of the reductant glutathione, cysteine, or NADPH capable of converting chromium(VI) to chromium(III) compounds (Bennicelli et al. 1983; De Flora 1978,1981). Chromium(VI) compounds caused gene mutations in *Bacillus subtilis* (Kanematsu et al. 1980; Nakamuro et al. 1978; Nishioka 1975) and *Escherichia coli* (Kanematsu et al. 1980; Kortenkamp et al. 1996b; Llagostera et al. 1986; Nakamuro et al. 1978; NTP 2007; Olivier and Marzin 1987; Venitt and Levy 1974; Watanabe et al. 1998a). Negative or weakly positive results were reported in *B. subtilis* with chromium(III) (Kanematsu et al. 1980; Matsui 1980; Nakamuro et al. 1978; Nishioka 1975) and mostly negative results were reported in *E. coli* (Llagostera et al. 1986; NTP 2008b; Olivier and Marzin 1987; Venier et al. 1989). However, hydrophobic ligands such as 2,2'-bipyridine, 1,10-phenanthroline, or picolinic acid form complexes with chromium(III), which are able to penetrate cell membranes and to cause genotoxicity. Complexes of chromium(III) with 2,2'-bipyridine or 1,10-phenanthroline were mutagenic in *S. typhimurium* (Warren et al. 1981). Chromium(III) picolinate was not mutagenic in *S. typhimurium* or *E. coli* (NTP 2008b).

A chromium(IV) ester was synthesized with 2,4-dimethyl-pentane-2,4-diol to examine its ability to cause DNA double strand breaks (Luo et al. 1996). Calf thymus DNA was reacted with the chromium(IV) complex (1.3 mg/mL) in the presence of 2 mM hydrogen peroxide for 6 days at pH 6.8. The results showed that the complex in the presence of hydrogen peroxide significantly damaged DNA by causing double strand breaks. Neither chromium(IV) or hydrogen peroxide alone damaged DNA. The kinetics of the reaction of chromium(IV) with hydrogen peroxide showed the formation of proportional amounts of hydroxyl radical with chromium(V). Use of a free radical scavenger prevented DNA strand breaks. Other studies have shown that chromium(IV) is a better Fenton reagent than chromium(V) for reducing hydrogen peroxide, and thus, chromium(IV)-type damage by generating hydroxyl radicals may also be a contributor of *in vivo* genotoxicity.

In conclusion, chromium(VI) compounds were positive in the majority of tests reported, and their genotoxicity was related to the solubility and, therefore, to the bioavailability to the targets. Results of occupational exposure studies in humans, although somewhat compromised by concomitant exposures to other potential genotoxic compounds, provide evidence of chromium(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks. Findings from occupational exposure studies are supported by results of *in vivo*

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studies in animals, *in vitro* studies in mammalian cells, yeast and bacteria, and studies in cell-free systems. Compared to chromium(VI), chromium(III) was more genotoxic in subcellular targets, but lost this ability in cellular systems. The reduction of chromium(VI) in the cells to chromium(III) and its subsequent genotoxicity may be greatly responsible for the final genotoxic effects (Beyersmann and Koster 1987; Zhitkovich et al. 2005). Reduction of chromium(VI) can also result in the formation of chromium(V), which is highly reactive and capable of interaction with DNA (Jennette 1982; Norseth 1986).

3.4 TOXICOKINETICS

The toxicokinetics of a given chromium compound depend on the valence state of the chromium atom and the nature of its ligands. Naturally occurring chromium compounds are generally in the trivalent state (chromium(III)), while hexavalent chromium compounds (chromium(VI)) are produced industrially by the oxidation of chromium(III) compounds.

The amount and location of deposition of inhaled chromium will be determined by factors that influence convection, diffusion, sedimentation, and interception of particles in the airways. These factors include air flow velocities, which are affected by breathing rate and tidal volume; airway geometry; and aerosol particle size (ICRP 1994). In general, deposition in the thoracic and pulmonary regions of the respiratory tract increase (as a fraction of the total deposited dose) as particle sizes decrease. Larger particles (e.g., >10 µm in diameter) deposit in the extrathoracic region. Chromium that deposits in the respiratory tract are subject to three general clearance processes: (1) mucociliary transport to the gastrointestinal tract for the ciliated airways (i.e. trachea, bronchi, and proximal bronchioles); (2) phagocytosis by lung macrophages and cellular transport to thoracic lymph nodes; or (3) absorption and transfer by blood and/or lymph to other tissues. The above processes apply to all forms of deposited chromium, although the relative contributions of each pathway and rates associated with each pathway may vary with the physical characteristics (e.g., particle size), chemical form (degree of water solubility), and chemotactic properties of the chromium particles. In general, less water-soluble chromium compounds that deposit in the pulmonary region can be expected to have a longer retention time in the lung than more soluble forms. In addition, lung concentrations of chromium increase with increasing age.

Most quantitative studies of the gastrointestinal absorption of chromium in humans have estimated the absorption fraction to be <10% of the ingested dose. In general, these studies suggest that the absorption fraction of soluble chromium compounds is higher than insoluble forms (e.g., CrCO₃), and is higher for

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soluble chromium(VI) compounds (e.g., $K_2Cr_2O_7$) than soluble chromium(III) (e.g., $CrCl_3$).

Chromium(VI) is reduced in the stomach to chromium(III), which lowers the absorbed dose from ingested chromium(VI). Absorption is also affected by the nutritional status of chromium(III); the absorption fraction is higher when dietary intakes are lower. Peak plasma concentrations of chromium occur within 2 hours following an oral dose of soluble chromium, suggesting that absorption occurred. Chromium absorption occurs in the upper small intestine.

Chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Few quantitative estimates of dermal absorption in humans have been reported. A 3-hour immersion in a warm aqueous bath of 22 mg Cr(VI)/L (as $K_2Cr_2O_7$) resulted in absorption (based on urine measurements) of approximately 3.3×10^{-5} – 4.1×10^{-4} μg Cr/cm²-hour (Corbett et al. 1997).

Absorbed chromium distributes to nearly all tissues, with the highest concentrations found in kidney and liver. Bone is also a major depot and may contribute to long-term retention kinetics of chromium. Chromium(VI) is unstable in the body and is reduced to chromium(V), chromium(IV), and ultimately to chromium(III) by many substances including ascorbate and glutathione. Reduction of chromium(VI) to chromium(III) can give rise to reactive intermediates, chromium adducts with proteins and DNA, and secondary free radicals. Chromium(VI) in blood is taken up into red blood cells, where it undergoes reduction and forms complexes with hemoglobin and other intracellular proteins that are sufficiently stable to retain chromium for a substantial fraction of the red blood cell lifetime. Absorbed chromium can be transferred to fetuses through the placenta and to infants via breast milk. Absorbed chromium is excreted predominantly in urine. Studies in animals have shown that chromium can be secreted in bile following parenteral (e.g., intravenous) injection of chromium(VI) or chromium(III) compounds. Chromium can also be eliminated by transfer to hair and nails. Chromium absorbed following ingestion of chromium(VI) (as $K_2Cr_2O_7$) appears to have a slower elimination rate ($t_{1/2}$ approximately 40 hours) than when chromium is absorbed following ingestion of soluble chromium(III) (as $CrCl_3$; $t_{1/2}$ approximately 10 hours).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages.

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The identification of chromium in urine, serum and tissues of humans occupationally exposed to soluble chromium(III) or chromium(VI) compounds in air indicates that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). In most cases, chromium(VI) compounds are more readily absorbed from the lungs than chromium(III) compounds, due in part to differences in the capacity to penetrate biological membranes. Nevertheless, workers exposed to chromium(III) lignosulfonate dust at 0.005–0.23 mg chromium(III)/m³ had clearly detectable concentrations of chromium in the urine at the end of their shifts. Based on a one-compartment kinetic model, the biological half-life of chromium(III) from the lignosulfonate dust was 4–10 hours, which is the same order of magnitude as the half-life for chromium(VI) compounds (Kiilunen et al. 1983).

Rats exposed to 2.1 mg chromium(VI)/m³ as zinc chromate 6 hours/day achieved steady-state concentrations in the blood after ~4 days of exposure (Langård et al. 1978). Rats exposed for a single inhalation of chromium(VI) trioxide mist from electroplating at a concentration of 3.18 mg chromium(VI)/m³ for 30 minutes rapidly absorbed chromium from the lungs. The content of chromium in the lungs declined from 13.0 mg immediately after exposure to 1.1 mg at 4 weeks in a triphasic pattern with an overall half-life of 5 days (Adachi et al. 1981). Based on a study in rats exposed to chromium(VI) as potassium dichromate or to chromium(III) as chromium trichloride, the pulmonary clearance of both valence states was dependent on particle size, and chromium(VI) was more rapidly and extensively transported to the bloodstream than chromium(III). The rats had been exposed to 7.3–15.9 mg chromium(VI)/m³ as potassium dichromate for 2–6 hours or to 8 or 10.7 mg chromium(III)/m³ as chromium trichloride for 6 or 2 hours, respectively. Chromium(VI) particles of 1.5 or 1.6 µm had a two-compartment pulmonary clearance curve with half-lives of 31.5 hours for the first phase and 737 hours for the second phase. Chromium(VI) particles of 2 µm had a single component curve with a half-life between 151 and 175 hours. Following exposure to chromium(VI), the ratio of blood chromium/lung chromium was 1.44 at 0.5 hours, 0.81 at 18 hours, 0.85 at 48 hours, and 0.96 at 168 hours after exposure. Chromium(III) particles of 1.5–1.8 µm had a single component pulmonary clearance curve with a half-life of 164 hours. Following exposure to chromium(III), the ratio of blood chromium/lung chromium was 0.39 at 0.5 hours, 0.24 at 18 hours, 0.22 at 48 hours, and 0.26 at 168 hours after exposure. Therefore, the amount of chromium(VI) transferred to the blood from the lungs was always at least 3 times greater than the amount of chromium(III) transferred (Suzuki et al. 1984). Other studies reporting absorption from the lungs are intratracheal injection studies (Baetjer et al. 1959b; Bragt and van Dura 1983; Vissek et al. 1953; Wiegand et al. 1984, 1987). These studies indicate that 53–85% of chromium(VI) compounds (particle

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size $<5\ \mu\text{m}$) are cleared from the lungs by absorption into the bloodstream or by mucociliary clearance in the pharynx; the rest remain in the lungs. Absorption by the bloodstream and mucociliary clearance was only 5–30% for chromium(III) compounds.

The kinetics of three chromium(VI) compounds, sodium chromate, zinc chromate, and lead chromate, were compared in rats in relation to their solubility. The rats received intratracheal injections of the $^{51}\text{chromium}$ -labeled compounds (0.38 mg chromium(VI)/kg as sodium chromate, 0.36 mg chromium(VI)/kg as zinc chromate, or 0.21 mg chromium(VI)/kg as lead chromate). Peak blood levels of $^{51}\text{chromium}$ were reached after 30 minutes for sodium chromate ($0.35\ \mu\text{g chromium/mL}$), and 24 hours for zinc chromate ($0.60\ \mu\text{g chromium/mL}$) and lead chromate ($0.007\ \mu\text{g chromium/mL}$). At 30 minutes after administration, the lungs contained 36, 25, and 81% of the respective dose of the sodium, zinc, and lead chromate. On day 6, $>80\%$ of the dose of all three compounds had been cleared from the lungs, during which time, the disappearance from lungs followed linear first-order kinetics. The residual amounts left in the lungs on day 50 or 51 were 3.0, 3.9, and 13.9%, respectively. The results indicate that zinc chromate, which is $\sim 1,000$ times less soluble than sodium chromate, is more slowly absorbed from the lungs, but peak blood levels are higher than sodium chromate. Lead chromate was more poorly and slowly absorbed, as indicated by very low levels in blood and other tissues, and greater retention in the lungs (Bragt and van Dura 1983).

The fate of lead chromate(VI), chromium(VI) trioxide, chromium(III) oxide and chromium(III) sulfate were examined when solutions or suspensions of these chemicals were slowly infused into the tracheal lobe bronchus of sheep via bronchoscopic catheterization (Perrault et al. 1995). At 2, 3, 5, and 30 days, the samples of bronchoalveolar lavage were taken, and on day 31, the animals were sacrificed and lung specimens were examined for chromium particulates. There was no difference in lung particle concentrations among the four different compounds. The values ranged from 0.14×10^5 to 1.02×10^5 particles/g dry tissue compared to control values of 0.03×10^5 . The alveolar clearance of slightly soluble chromium(III) oxide and chromium(III) sulfate was calculated to be 11 and 80 days, respectively. The insoluble lead chromate particles appeared to break up, forming isometric particles of lead chromate as well as lead-containing particulates that may have retarded clearance. Retention of chromium particulates from exposure to soluble chromium trioxide may have resulted in the formation of a less-soluble hydroxyl complex and/or chemical interaction between chromium and protein that prolongs the retention of the metal. Analyses of the particulates in lavage samples indicate that these diameters increase with time for lead chromate, decrease with time for chromium sulfate and chromium trioxide, and are unchanged for chromium(III) oxide. The authors state that their findings indicate that slightly

soluble chromium(III) oxide and chromium sulfate that are chemically stable can be cleared from lungs at different rates, depending on the nature and morphology of the compound.

Amounts of total chromium were measured in lymphocytes, blood, and urine after intratracheal administration of either sodium dichromate(VI) or chromium(III) acetate hydroxide (a water-soluble chromium(III) compound) to male Wistar rats (Gao et al. 1993). The total amount of chromium administered was 0.44 mg chromium/kg body weight for each compound. The highest concentrations in tissues and urine occurred at 6 hours after treatment, the first time point examined. Mean chromium concentrations (n=4 rats per time point) from treatment with chromium(III) were 56.3 µg/L in whole blood, 96 µg/L in plasma, 0.44 µg/10¹⁰ in lymphocytes, and 4,535.6 µg/g creatinine in urine. For treatment with chromium(VI) the levels were 233.2 µg/L for whole blood, 138 µg/L for plasma, 2.87 µg/10¹⁰ for lymphocytes, and 2,947.9 µg/g creatinine in urine. The levels in lymphocytes in the chromium(III) treated animals were no different than in untreated animals. However, for chromium(VI) the lymphocyte levels were about 6-fold higher than control values. After 72 hours, the chromium levels were significantly reduced. These results suggest that absorbed chromium(III) compounds may be excreted more rapidly than absorbed chromium(VI) compounds because of a poorer ability to enter cells.

3.4.1.2 Oral Exposure

Chromium(III) is an essential nutrient required for normal energy metabolism. The Institute of Medicine (IOM 2001) of the NAS determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults (IOM 2001). Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as glucose tolerance factor (GTF), has been proposed as one possible candidate (Jacquemet et al. 2003). The function of chromodulin, an oligopeptide complex containing with four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven (Anderson 1998a, 2003; IOM 2001). Chromium(III) picolinate is a common form of chromium(III) nutritional supplementation.

Trivalent chromium is very poorly absorbed from the gastrointestinal tract. Typically, ≤1% of an orally administered dose of trivalent chromium has been recovered in the urine of experimental animals of humans (Aitio et al. 1984; Anderson et al. 1983; Doisy et al. 1971; Donaldson and Barreras 1966; Gargas et al. 1994; Garcia et al. 2001; Kerger et al. 1996a) or experimental animals (Donaldson and Barreras 1966; Febel et al. 2001). Oral absorption of trivalent chromium complexed with an organic ligand is

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similarly low and not higher than inorganic forms (Anderson et al. 1996; Gonzalez-Vergara et al. 1981). Bypassing the stomach by infusing trivalent chromium into the duodenum or jejunum resulted in at most 1–2% of the dose being absorbed in humans (Donaldson and Barreras 1966), or 1% (Febel et al. 2001) to 4% in the rat (Donaldson and Barreras 1966).

Approximately 0.5–2.0% of dietary chromium(III) is absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983) as inferred from urinary excretion measurements. The absorption fraction is dependent on the dietary intake. At low levels of dietary intake (10 µg), ~2.0% of the chromium was absorbed. When intake was increased by supplementation to ≥40 µg, the absorption decreased to ~0.5% (Anderson 1986; Anderson et al. 1983). Net absorption of chromium(III) by a group of 23 elderly subjects who received an average of 24.5 µg/day (0.00035 mg chromium(III)/kg/day) from their normal diets was calculated to be 0.6 µg chromium(III)/day, based on an excretion of 0.4 µg chromium/day in the urine and 23.9 µg chromium/day in the feces, with a net retention of 0.2 µg/day. Thus, about 2.4% was absorbed. The retention was considered adequate for their requirements (Bunker et al. 1984).

The absorption fraction of soluble chromium(III), as chromium picolinate, is greater than CrCl₃ (DiSilvestro and Dy 2007; Gargas et al. 1994). Following ingestion of 400 µg chromium(III)/day as chromium picolinate (in a capsule) for 3 consecutive days, mean absorption fraction in eight healthy adults was 2.8% (±1.4 % standard deviation [SD]; Gargas et al. 1994). Based on urinary excretion following oral administration of a single dose (200 µg chromium(III)) of four different chromium(III) supplements to healthy women (n=24; cross-over design), the absorption of chromium picolinate was higher than that of chromium chloride, chromium polynicotinate, and chromium nicotinate-glucinate; estimates of oral absorption were not reported (DiSilvestro and Dy 2007). Urinary excretion of chromium following administration of chromium picolinate was approximately 16-fold higher than that following administration of chromium chloride and approximately 2-fold greater than that following administration of the two nicotinate complexes.

Association of chromium with chelating agents, which may be naturally present in feed, can alter the bioavailability from food. In rats that were given ⁵¹Cr-chromium(III) trichloride mixed with chelating agents, either oxalate or phytate, phytate significantly (p<0.05) decreased the levels of radioactivity in blood, whole body, and urine achieved with chromium(III) trichloride alone (Chen et al. 1973). Oxalate, however, greatly increased the levels in blood, whole body, and urine. The oxalate served as a strong ligand to protect against the tendency of chromium(III) to form insoluble macromolecular chromium

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oxides at physiological pH. Fasted rats absorbed significantly more ⁵¹chromium than did nonfasted rats, indicating that the presence of food in the gastrointestinal tract slows the absorption of chromium. Results of an *in vitro* experiment in this study indicated that the midsection had greater uptake than the duodenum or ileum and that oxalate significantly ($p < 0.05$) increased, while phytate significantly ($p < 0.05$) decreased the transport of chromium(III) across all three sections, paralleling the *in vivo* results. Ethylenediamine tetraacetic acid (EDTA) and citrate were also tested in the *in vitro* system, but were found to have no effect on chromium(III) intestinal transport; therefore, these chelating agents were not tested *in vivo* (Chen et al. 1973).

The absorption fraction of soluble chromium(VI) is higher than that of soluble chromium(III) (Anderson et al. 1983; Donaldson and Barreras 1966; Kerger et al. 1996a). Average absorption fractions, determined from cumulative urinary excretion in 8 healthy adults who ingested 5 mg chromium (in 10 mg Cr/L drinking water) as CrCl₃ or K₂Cr₂O₇ were 0.13% (± 0.04 , standard error [SE]) and 6.9% (± 3.7 , SE), respectively. Chromium(VI) can be reduced to chromium(III) when placed in an ascorbic acid solution (Kerger et al. 1996a). When K₂Cr₂O₇ was ingested in orange juice (where it was reduced and may have formed complexes with constituents of the juice), the mean absorption fraction was 0.60% (± 0.11 , SE; Kerger et al. 1996a). Plasma concentrations generally peaked around 90 minutes following exposure for all three chromium mixtures tested. Based on measurements of urinary excretion of chromium in 15 female and 27 male subjects who ingested 200 μ g chromium(III) as CrCl₃, the absorption fraction was estimated to be approximately 0.4% (Anderson et al. 1983). The absorption fraction of chromium(VI) (as sodium chromate) was substantially higher when administered directly into the duodenum (approximately 10%) compared to when it is ingested (approximately 1.2%), whereas the absorption fraction for CrCl₃ was similar when administered into the small intestine (0.5%; Donaldson and Barreras 1966). These results are consistent with studies that have shown that gastric juice can reduce chromium(VI) to chromium(III) (De Flora et al. 1987a).

The absorption of chromium(VI) and chromium(III) was measured in four male and two female volunteers (ages ranging from 25 to 39 years) treated orally with potassium chromate (chromium(VI)) or chromic oxide (chromium(III)) in capsules at doses of 0.005 and 1.0 mg/kg/day, respectively (Finley et al. 1996b). Subjects were exposed to each compound for 3 days. Based on urinary excretion data, the mean absorption of potassium chromate was 3.4% (range 0.69–11.9%). No statistically significant increase in urinary chromium was observed during chromic oxide dosing, indicating that little, if any, was absorbed. In a follow-up study by the same group (Finley et al. 1997), five male volunteers ingested a liter, in three volumes of 333 mL, of deionized water containing chromium(VI) concentrations ranging from 0.1 to

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10.0 mg/L (approximately 0.001–0.1 mg chromium(VI)/kg/day) for 3 days. A dose-related increase in urinary chromium was seen in all subjects and the percent of the dose excreted ranged from <2 to 8%. Dose-related increases in plasma and erythrocyte chromium levels were also observed.

In a repeated dose study, three healthy adults ingested chromium(VI) (as $K_2Cr_2O_7$) in water at 5 mg chromium/day for 3 consecutive days (Kerger et al. 1997). Three divided doses were taken at approximately 6-hour intervals over a 5–15-minute period. After at least 2 days without dosing, the 3-day exposure regimen was repeated at 10 mg chromium/day. Estimated doses based on body weight were 0.05 and 0.1 mg/kg/day, respectively. Bioavailability based on 4-day urinary excretion was 1.7% (range 0.5–2.7%) at 0.05 mg chromium(VI)/kg/day and 3.4% (range 0.8–8.0%) at 0.1 mg chromium(VI)/kg/day. Absorption of 0.05 mg chromium(VI)/kg appeared to be somewhat lower when given as three divided doses rather than when given as a single bolus dose (1.7 versus 5.7%).

Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days. Red blood cell and plasma levels returned to background levels within a few days after exposure was stopped. The data are consistent with a bioavailability of 2% and a plasma elimination half-life of 36 hours.

Studies with 51 chromium in animals indicate that chromium and its compounds are also poorly absorbed from the gastrointestinal tract after oral exposure. When radioactive sodium chromate (chromium(VI)) was given orally to rats, the amount of chromium in the feces was greater than that found when sodium chromate was injected directly into the jejunum. Since chromium(III) is absorbed less readily than chromium(VI) by the gastrointestinal tract, these results are consistent with evidence that the gastric environment has a capacity to reduce chromium(VI) to chromium(III). *Ex vivo* studies in rats and mice demonstrate that the reduction of chromium(VI) to chromium(III) in the stomach follows second-order kinetics and that the reduction rate is concentration-dependent and capacity-limited (Proctor et al. 2012). The investigators estimated second-rate constants of 0.3 L/mg·hour for rats and 0.2 L/mg·hour for mice and total reducing capacities of 15.7 and 16.6 mg chromium(VI) equivalents/L of stomach contents, respectively.

The administration of radioactive chromium(III) or chromium(VI) compounds directly into the jejunum decreased the amount of chromium recovery in the feces indicating that the jejunum is the absorption site for chromium (Donaldson and Barreras 1966). Absorption of either valence state was $\leq 1.4\%$ of the

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administered oral dose in rats (Sayato et al. 1980) and hamsters (Henderson et al. 1979). Based on distribution (see Section 3.3.2.2) and excretion (see Section 3.3.4.2) studies in rats administered chromium by gavage for 2–14 days from various sources, that is, from sodium chromate (chromium(VI)), from calcium chromate (chromium(VI)), or from soil contaminated with chromium (30% chromium(VI) and 70% chromium(III)), the low gastrointestinal absorption of chromium from any source was confirmed. Chromium appeared to be better absorbed from the soil than from chromate salts, but <50% of the administered chromium could be accounted for in these studies, partly because not all tissues were examined for chromium content and excretion was not followed to completion (Witmer et al. 1989, 1991). Adult and immature rats given chromium(III) chloride absorbed 0.1 and 1.2% of the oral dose, respectively (Sullivan et al. 1984). This suggests that immature rats may be more susceptible to potential toxic effects of chromium(III) compounds.

Treatment of rats by gavage with a nonencapsulated lead chromate pigment or with a silica-encapsulated lead chromate pigment resulted in no measurable blood levels of chromium (detection limit=10 µg/L) after 2 or 4 weeks of treatment or after a 2-week recovery period. However, kidney levels of chromium were significantly higher in the rats that received the nonencapsulated pigment than in the rats that received the encapsulated pigment, indicating that silica encapsulation reduces the gastrointestinal bioavailability of chromium from lead chromate pigments (Clapp et al. 1991).

The issue of whether or not chromium(VI) absorption occurs only when or principally when the reducing capacity of the gastrointestinal tract is exhausted is a factor to consider in evaluating and interpreting oral dosing bioassays in animals and human epidemiology studies of health outcomes related to ingestion exposures to chromium. Potentially, tumor responses could be enhanced if the reducing capacities of saliva and stomach fluid were exhausted. This is more likely to occur at the relatively high doses of chromium(VI) administered in animal bioassays than at doses experienced by humans from environmental exposures. However, results of experimental studies of chromium absorption in humans have not found evidence for an effect of limited reducing capacity on absorption of chromium. The range of doses of chromium administered to humans in these different studies was considerable and demonstrated oral bioavailability at all doses. Donaldson and Barreras (1996) administered 20 ng of radiolabeled chromium(VI), Kerger et al. (1996a) administered 5 mg of chromium(VI), Finley et al. (1996b) administered 0.005 mg/kg/day of chromium(VI) for 3 days, and Finley et al. (1997) administered 0.1, 0.5, 1.0, 5.0 or 10 mg/day of chromium(VI) for 4 days. In the Finley et al. (1997) study, the percent of the administered dose of chromium(VI) recovered in the urine did not increase with dose. The results of these studies do not indicate that oral absorption of administered chromium(VI) only begins to occur

when the reducing capacity of the stomach is exhausted, and are consistent with estimates of gastrointestinal reducing capacity (De Flora 2000; Proctor et al. 2002).

3.4.1.3 Dermal Exposure

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Systemic toxicity has been observed in humans following dermal exposure to chromium compounds, indicating significant cutaneous absorption (see Section 3.2.3). Fourteen days after a salve containing potassium chromate was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood, urine, feces, and stomach contents (Brieger 1920) (see Section 3.4.2.3). It should be noted that the preexisting condition of scabies or the necrosis caused by the potassium chromate (see Section 3.2.3) could have facilitated dermal absorption of potassium chromate. Potassium dichromate (chromium(VI)), but not chromium(III) sulfate, penetrated the excised intact epidermis of humans (Mali et al. 1963). Dermal absorption by humans of chromium(III) sulfate in aqueous solution was negligible, with slightly larger amounts of chromium(III) nitrate in aqueous solution absorbed. The absorption of chromium(III) chloride was similar to potassium dichromate(VI) (Samitz and Shrager 1966). Chromium(III) from a concentrated chromium sulfate solution at pH 3 penetrated cadaverous human skin at a rate of 5×10^{-11} cm/sec, compared with a rate for chromium(VI) (source unspecified) of 5×10^{-7} cm/second (Spruit and van Neer 1966). In contrast, both chromium(VI) from sodium chromate and chromium(III) from chromium trichloride penetrated excised human mammary skin at similar rates, but the rate was generally slightly faster for chromium(VI). Absolute rates of absorption in nmol chromium/hour/cm² increased with increasing concentration of both chromium(VI) and chromium(III) (Wahlberg 1970). The average rate of systemic uptake of chromium in four volunteers submersed up to the shoulders in a tub of chlorinated water containing a 22 mg chromium(VI)/L solution of potassium dichromate for 3 hours was measured to be 1.5×10^{-4} µg/cm²-hour based on urinary excretion of total chromium (Corbett et al. 1997).

The influence of solvent on the cutaneous penetration of potassium dichromate by humans has been studied. The test solutions of potassium dichromate in petrolatum or in water were applied as occluded circular patches of filter paper to the skin. Results with dichromate in water revealed that chromium(VI) penetrated beyond the dermis and penetration reached steady state with resorption by the lymph and blood vessels by 5 hours. About 10 times more chromium penetrated when potassium dichromate was applied in petrolatum than when applied in water. About 5 times more chromium penetrated when potassium dichromate was applied than when a chromium trichloride glycine complex was applied (Liden

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and Lundberg 1979). The rates of absorption of solutions of sodium chromate from the occluded forearm skin of volunteers increased with increasing concentration. The rates were 1.1 $\mu\text{g chromium(VI)}/\text{cm}^2/\text{hour}$ for a 0.01 M solution, 6.4 $\mu\text{g chromium(VI)}/\text{cm}^2/\text{hour}$ for a 0.1 M solution, and 10 $\mu\text{g chromium(VI)}/\text{cm}^2/\text{hour}$ for a 0.2 M solution (Baranowska-Dutkiewicz 1981).

Chromium and its compounds are also absorbed dermally by animals. The dermal absorption of sodium chromate (chromium(VI)) by guinea pigs was somewhat higher than that of chromium(III) trichloride, but the difference was not significant. At higher concentrations (0.261–0.398 M), absorption of sodium chromate was statistically higher than that of chromium trichloride. The peak rates of absorption were 690–725 and 315–330 $\text{nmol}/\text{hour}/\text{cm}^2$ for sodium chromate at 0.261–0.398 M and chromium trichloride at 0.239–0.261 M, respectively. Percutaneous absorption of sodium chromate was higher at $\text{pH} \geq 6.5$ compared with $\text{pH} \leq 5.6$ (Wahlberg and Skog 1965).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Examination of tissues from Japanese chrome platers and chromate refining workers at autopsy revealed higher chromium levels in the hilar lymph node, lung, spleen, liver, kidney, and heart, compared to normal healthy males (Teraoka 1981). Analysis of the chromium concentrations in organs and tissues at autopsy of a man who died of lung cancer 10 years after his retirement from working in a chromate producing plant for 30 years revealed measurable levels in the brain, pharyngeal wall, lung, liver, aorta, kidney, abdominal rectal muscle, suprarenal gland, sternal bone marrow, and abdominal skin. The levels were significantly higher than in five controls with no occupational exposure to chromium. The man had been exposed mainly to chromium(VI), with lesser exposure to chromium(III) as the chromite ore (Hyodo et al. 1980). The levels of chromium were higher in the lungs, but not in the liver or kidneys, of autopsy specimens from 21 smeltery and refinery workers in North Sweden compared with that for a control group of 8 individuals. The amount of enrichment in the lungs decreased as the number of elapsed years between retirement and death increased (Brune et al. 1980). Tissues from three individuals having lung cancer who were industrially exposed to chromium were examined by Mancuso (1997b). One was employed for 15 years as a welder, a second worked for 10.2 years, and a third for 31.8 years in ore milling and preparations and boiler operations. The three cumulative chromium exposures for the three workers were 3.45, 4.59, and 11.38 mg/m^3 years, respectively. Tissues from the first worker were analyzed 3.5 years after last exposure, the second worker 18 years after, and the third worker 0.6 years after last exposure. All tissues from the three workers had elevated levels of chromium with the possible

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exception of neural tissues. Levels were orders of magnitude higher in lungs than other tissues. The highest lung level reported was 456 mg/10 g tissue in the first worker, 178 in the second worker, and 1,920 for the third worker. There were significant chromium levels in the tissue of the second worker even though he had not been exposed to chromium for 18 years. Chromium concentrations in lung tissues from autopsy samples were 5 times higher in subjects who originated from the Ruhr and Dortmund regions of Germany, where emissions of chromium are high, than in subjects from Munster and vicinity. The lung concentrations of chromium increased with increasing age. Men had twice as high concentrations of chromium in the lungs than did women, which may reflect the greater potential for occupational exposure by men, the higher vital capacity of men, and possibly a greater history of smoking (Kollmeier et al. 1990).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Analysis of chromium levels in women employees of a dichromate manufacturing facility in Russia during and after pregnancy revealed that the exposed women had significantly higher levels of chromium in blood and urine during pregnancy, in umbilical cord blood, placentae, and breast milk at child birth, and in fetuses aborted at 12 weeks than did nonexposed controls (Shmitova 1980). The reliability of this study is suspect because the levels of chromium reported in the blood and urine of the control women were much higher than usual background levels of chromium in these biological fluids (see Section 6.5), perhaps due to problems with analytical methods. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained $<0.4 \mu\text{g/L}$, and the mean value was $0.3 \mu\text{g/L}$ (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk.

The distribution of radioactivity in rats given $^{51}\text{chromium}$ as sodium dichromate intratracheally was followed for 40 days by autoradiography and scintillation counting. Three days after the administration of $0.01 \text{ mg chromium(VI)/m}^3$ as radioactive sodium dichromate, the tissue distribution based on the relative concentrations in the tissue was lung > kidney > gastrointestinal tract > erythrocytes > liver > serum > testis > skin. Twenty-five days after dosing, the tissue distribution was lung > kidney > erythrocytes > testis > liver > serum > skin > gastrointestinal tract. Kidney, erythrocytes, and testis maintained their chromium levels for a period of 10–15 days before decreasing (Weber 1983). The distribution of chromium(VI) compared with chromium(III) was investigated in guinea pigs after intratracheal instillation of potassium dichromate or chromium trichloride. At 24 hours after instillation, 11% of the original dose of chromium from potassium dichromate remained in the lungs, 8% in the

erythrocytes, 1% in plasma, 3% in the kidney, and 4% in the liver. The muscle, skin, and adrenal glands contained only a trace. All tissue concentrations of chromium declined to low or nondetectable levels in 140 days with the exception of the lungs and spleen. After chromium trichloride instillation, 69% of the dose remained in the lungs at 20 minutes, while only 4% was found in the blood and other tissues, with the remaining 27% cleared from the lungs and swallowed. The only tissue that contained a significant amount of chromium 2 days after instillation of chromium trichloride was the spleen. After 30 and 60 days, 30 and 12%, respectively, of the chromium(III) was retained in the lungs, while only 2.6 and 1.6%, respectively, of the chromium(VI) dose was retained in the lung (Baetjer et al. 1959a).

3.4.2.2 Oral Exposure

Autopsy studies in the United States indicate that chromium concentrations in the body are highest in kidney, liver, lung, aorta, heart, pancreas, and spleen at birth and tend to decrease with age. The levels in liver and kidney declined after the second decade of life. The aorta, heart, and spleen levels declined rapidly between the first 45 days of life and 10 years, with low levels persisting throughout life. The level in the lung declined early, but increased again from mid life to old age (Schroeder et al. 1962).

The distribution of chromium in human body tissue after acute oral exposure was determined in the case of a 14-year-old boy who ingested 7.5 mg chromium(VI)/kg as potassium dichromate. Despite extensive treatment by dialysis and the use of the chelating agent British antilewisite, the boy died 8 days after admission to the hospital. Upon autopsy, the chromium concentrations were as follows: liver, 2.94 mg/100 cc (normal, 0.016 mg/100 cc); kidneys, 0.64 and 0.82 mg/100 cc (normal, 0.06 mg/100 cc); and brain, 0.06 mg/100 cc (normal, 0.002 mg/100 cc) (Kaufman et al. 1970). Although these data were obtained after extensive treatment to rid the body of excess chromium, the levels of chromium remaining after the treatment clearly demonstrate that these tissues absorbed at least these concentrations after an acute, lethal ingestion of a chromium(VI) compound.

Chromium may be transferred to infants via breast milk as indicated by breast milk levels of chromium in women exposed occupationally (Shmitova 1980) or via normal levels in the diet (Casey and Hambidge 1984). It has been demonstrated that in healthy women, the levels of chromium measured in breast milk are independent of serum chromium levels, urinary chromium excretion, or dietary intake of chromium (Anderson et al. 1993, Mohamedshah et al. 1998), but others (Engelhardt et al. 1990) have disputed this observation.

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The tissue distribution of chromium was studied in rats administered chromium from a variety of sources. In one experiment, sodium chromate in water was administered by gavage for 7 days at 0, 1.2, 2.3, or 5.8 mg chromium(VI)/kg/day. Very little chromium (generally <0.5 $\mu\text{g}/\text{organ}$) was found in the organs analyzed (liver, spleen, lung, kidney, and blood) after administration of the two lower doses. The levels were generally comparable to those in controls. After 5.8 mg/kg/day, the largest amount of chromium (expressed as μg chromium/whole organ) was found in the liver (≈ 22 μg), followed by the kidney (≈ 7.5 μg), lung (≈ 4.5 μg), blood (≈ 2 μg), and spleen (≈ 1 μg). The total amount of chromium in these tissues represented only 1.7% of the final dose of 5.8 mg/kg/day, but not all organs were analyzed. In the next experiment, rats were exposed by gavage to 7 mg chromium/kg/day for 7 days from various sources: (1) sodium chromate; (2) calcium chromate; (3) soil containing chromium (30% chromium(VI), 70% chromium(III)); or (4) a mixture of calcium chromate and the contaminated soil. The highest levels of chromium were found in liver, spleen, kidney, lung, blood, brain, and testes after dosing with sodium chromate, but the relative levels in these tissues after the other treatments followed no consistent pattern. Rats gavaged for 14 days with 13.9 mg chromium/kg/day from the four different sources had higher levels of chromium in the tissues after they were dosed with the contaminated soil or the mixture of calcium chromate and the contaminated soil than with either of the chromate salts alone. Thus, the relative organ distribution of chromium depends on the source of chromium (Witmer et al. 1989, 1991). Components in soil may affect the oxidation state and the binding of chromium to soil components, and pH of the soil may also affect the bioavailability from soil.

The chromium content in major organs (heart, lung, kidney, liver, spleen, testes) of mice receiving drinking water that provided doses of 4.8, 6.1, or 12.3 mg chromium(III)/kg/day as chromium trichloride or 4.4, 5.0, or 14.2 mg chromium(VI)/kg/day as potassium dichromate was determined after 1 year of exposure. Chromium was detected only in the liver in the chromium(III)-treated mice. Mice treated with chromium(VI) compounds had accumulation in all of the above organs, with the highest levels reported in the liver and spleen. Liver accumulation of chromium was 40–90 times higher in the chromium(VI)-treated group than in the chromium(III)-treated group (Maruyama 1982). Chromium levels in tissue (bone, kidney liver, spleen) were 9 times higher in rats given chromium(VI) as potassium chromate in drinking water for 1 year than in rats given the same concentration of chromium(III) as chromium trichloride (MacKenzie et al. 1958). In rats exposed to potassium chromate in the drinking water for 3 or 6 weeks, a general trend of increasing chromium concentration with time of exposure was apparent in the liver and kidneys, but only the kidneys showed a difference in the concentration after exposure to 100 and 200 ppm. Blood concentrations were almost saturated by 3 weeks with little further accumulation by 6 weeks. No chromium was detected in the lungs after drinking water exposure (Coogan et al. 1991a).

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After acute oral dosing with radiolabeled chromium trichloride (1 μ Ci for immature rats, 10 μ Ci for adults), adult and neonatal rats accumulated higher levels of chromium in the kidneys than in the liver. At 7 days after dosing, the liver and kidney contained 0.05 and 0.12% of the dose, respectively, in the neonates and 0.002 and 0.003% of the dose, respectively, in the adult rats. The carcass contained 0.95% of the dose in the neonates and 0.07% of the dose in adult rats. The lungs contained 0.0088% of the dose in neonates and 0.0003% of the dose in adult rats. No chromium(III) was detected in the skeleton or muscle. Approximately 35 and 0.2% of the administered dose of chromium(III) at day 7 was retained in the gut of neonates and adults, respectively (Sullivan et al. 1984).

The distribution of potassium chromate(VI) was compared in male Fisher rats and C57BL/6J mice exposed either by drinking water (8 mg chromium(VI)/kg/day for 4 and 8 weeks) or by intraperitoneal injection (0.3 and 0.8 mg chromium(VI)/kg/day for 4 or 14 days) (Kargacin et al. 1993). The concentrations of chromium (μ g/g wet tissue) after drinking water exposures for 8 weeks in mice were: liver 13.83, kidney 4.72, spleen 10.09, femur 12.55, lung 1.08, heart 1.02, muscle 0.60, and blood 0.42. These concentrations were not markedly different than for 4-week exposures. For rats, the concentrations were: liver 3.59, kidney 9.49, spleen 4.38, femur 1.78, lung 0.67, heart 1.05, muscle 0.17, and blood 0.58. These results demonstrate that considerable species differences exist between mice and rats and need to be factored into any toxicological extrapolations across species even if the routes of administration are the same. In the drinking water experiments, blood levels in rats and mice were comparable, but in intraperitoneal injection experiments, rats' levels were about 8-fold higher than mice after 4 days of exposure. This difference appeared to be due to increased sequestering by rat red blood cells, since accumulation in white blood cells was lower in rats than mice. The higher incidence of red cell binding was also associated with greater binding of chromium to rat hemoglobin.

The feeding of five male Wistar rats at 0.49 mg chromium(III)/kg/day as chromium(III) chloride for 10 weeks resulted in increased chromium levels in liver, kidney, spleen, hair, heart, and red blood cells (Aguilar et al. 1997). Increases were highest in kidney (0.33 μ g/g wet tissue in controls versus 0.83 μ g/g in treated animals) and erythrocytes (1.44 μ g/g wet tissue in controls versus 3.16 μ g/g in treated animals).

The higher tissue levels of chromium after administration of chromium(VI) than after administration of chromium(III) (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991) reflect the greater tendency of chromium(VI) to traverse plasma membranes and bind to intracellular proteins in the various tissues, which may explain the greater degree of toxicity associated with chromium(VI). In an experiment to determine the distribution of chromium in red and white blood cells, rats were exposed

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orally to 0.0031 mg/kg of $^{51}\text{chromium(VI)}$ as sodium chromate. The $^{51}\text{chromium}$ content of the fractionated blood cells was determined either 24 hours or 7 days after exposure. After 24 hours, the white blood cells contained much more $^{51}\text{chromium}$ (≈ 250 pg chromium/billion cells) than did the red blood cells (≈ 30 pg chromium/billion cells). After 7 days, the $^{51}\text{chromium}$ content of the white blood cells was reduced only 2.5-fold, while that of the red blood cells was reduced 10-fold. Thus, white blood cells preferentially accumulated chromium(VI) and retained the chromium longer than did the red blood cells. As discussed in Section 3.4.2.4, a small amount of chromium(III) entered red blood cells of rats after intravenous injection of $^{51}\text{chromium trichloride}$, but no $^{51}\text{chromium}$ was detectable in white blood cells (Coogan et al. 1991b).

Twelve pregnant female albino rats (Druckrey strain) and 13 Swiss albino mice were exposed to 500 ppm potassium dichromate(VI) in their drinking water during pregnancy up to 1 day before delivery (Saxena et al. 1990a). The chromium(VI) daily intake was calculated to be 11.9 mg chromium(VI)/day for the rats and 3.6 mg chromium(VI)/day for mice which were considered to be maximal nontoxic doses for both species. In rats, concentrations of chromium were 0.067, 0.219, and 0.142 $\mu\text{g/g}$ fresh weight in maternal blood, placenta, and fetuses, respectively, and 0.064, 0.304, and 0.366 $\mu\text{g/g}$ fresh weight in mice, respectively. In treated rats, chromium levels were 3.2-fold higher in maternal blood, 3-fold higher in placenta, and 3.1-fold higher in fetal tissue when compared to control values. In treated mice, chromium levels were 2.5-fold higher in maternal blood, 3.2-fold higher in placenta, and 9.6-fold higher in fetuses when compared to control values. In treated mice, there was a significant elevation in chromium levels in placental and fetal tissues over maternal blood levels, and a significant increase in chromium levels in fetal tissue over placental concentrations when compared to controls. These differences were not observed in rats, indicating that the distribution patterns in mice and rats are different.

A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form. Male and female rats were fed either a commercial diet that contained 500 ppb chromium or a 30% Torula yeast diet that contained <100 ppb chromium. They were also given drinking water with or without 2 ppm chromium(III) added as chromium acetate monohydrate. The rats were mated and immediately after delivery, the neonates were analyzed for chromium content. The neonates whose dams were fed the commercial diet contained almost twice as much chromium as those whose dams were fed the chromium-deficient yeast diet. Addition of chromium(III) acetate to the drinking water of the yeast-fed rats (2 ppm) did not increase the levels of chromium in the neonates. Administration of chromium(III) trichloride intravenously or by gavage before mating, during mating, or during gestation resulted in no or only a small amount of chromium in the neonates. Administration of

chromium(III) in the form of GTF from Brewer's yeast by gavage during gestation resulted in chromium levels in the litters that were 20–50% of the dams' levels. The results indicate that fetal chromium is derived from specific chromium complexes in the diet (e.g., GTF) (Mertz et al. 1969).

3.4.2.3 Dermal Exposure

The findings of toxic effects in the heart, stomach, blood, muscles, and kidneys of humans who were dermally exposed to chromium compounds is suggestive of distribution to these organs (see Section 3.2.3.2). Fourteen days after a salve containing potassium chromate(VI) was applied to the skin of an individual to treat scabies, appreciable amounts of chromium were found in the blood (2–5 mg/100 mL), urine (8 mg/L), feces (0.61 mg/100 g), and stomach contents (0.63 mg/100 mL) (Brieger 1920). The preexisting condition of scabies or the necrosis caused by the potassium chromate could have facilitated its absorption. A transient increase in the levels of total chromium in erythrocytes and plasma was observed in subjects immersed in a tank of chlorinated water containing potassium dichromate(VI) (Corbett et al. 1997).

Chromium compounds are absorbed after dermal administration by guinea pigs. Measurement of ⁵¹chromium in the organs and body fluids revealed distribution, due to dermal absorption of chromium(III) and chromium(VI) compounds, to the blood, spleen, bone marrow, lymph glands, urine, and kidneys. Absorption was greater for chromium(VI) than for chromium(III) (see Section 3.4.1.3) (Wahlberg and Skog 1965).

3.4.2.4 Other Routes of Exposure

The distribution of chromium(III) in humans was analyzed using a whole-body scintillation scanner, whole-body counter, and plasma counting. Six individuals given an intravenous injection of ⁵¹chromium(III) as chromium trichloride had >50% of the blood plasma chromium(III) distributed to various body organs within hours of administration. The liver and spleen contained the highest levels. After 3 months, the liver contained half of the total body burden of chromium. The study results indicated a three-compartment model for whole-body accumulation and clearance of chromium(III). The half-lives were 0.5–12 hours for the fast component, 1–14 days for the medium component, and 3–12 months for the slow component (Lim et al. 1983).

An *in vitro* study in human blood showed that chromium(VI) was rapidly cleared from the plasma (Corbett et al. 1998). The reduction capacity appears to be concentration dependent and is overwhelmed

at spike concentrations between 2,000 and 10,000 µg/L. High chromium(VI) concentrations (10,000 µg/L spike concentration) resulted in an accumulation of chromium(VI) in the erythrocytes and a lower plasma:erythrocyte ratio of total chromium. This study also found that the plasma reduction capacity was enhanced by a recent meal.

Both human and rat white blood cells accumulated more ⁵¹chromium per cell than red blood cells after *in vitro* exposure of whole blood to ⁵¹chromium(VI). The uptake of chromium by rat blood cells was also measured after intravenous exposure to ⁵¹chromium(VI) as sodium chromate. After intravenous exposure, the white blood cells contained significantly more ⁵¹chromium (≈30 pg chromium/billion cells) than the red blood cells (≈4 pg chromium/billion cells), and the amount of ⁵¹chromium in the cells was the same after 24 hours as it was after 1 hour. The amount of ⁵¹chromium in the white blood cells, but not in the red blood cells, decreased by approximately 1.7-fold after 7 days. When rats were injected intravenously with 20 ng of radiolabeled sodium chromate (chromium(VI)) or radiolabeled chromium trichloride (chromium(III)), the amount of chromium was ≈2 pg/billion red blood cells but not detectable in white blood cells after injection of chromium(III) chloride. The amount of chromium was ≈5 pg/billion red blood cells and ≈60 pg/billion white blood cells after injection of sodium chromate (Coogan et al. 1991b).

The distribution pattern in rats treated with sodium chromite (chromium(III)) by intravenous injection revealed that most of the chromium was concentrated in the reticuloendothelial system, which, together with the liver, accumulated 90% of the dose. The accumulation in the reticuloendothelial system was thought to result from colloid formation by chromite at physiological pH. Organs with detectable chromium levels 42 days postinjection were: spleen > liver > bone marrow > tibia > epiphysis > lung > kidney. Chromium trichloride given to rats by intravenous injection also concentrated in the liver, spleen, and bone marrow (Vissek et al. 1953). In rats administered chromium(III) nitrate intraperitoneally for 30 or 60 days, the highest levels of chromium were found in the liver, followed by the kidneys, testes, and brain. The levels increased with increased doses but not linearly. The levels in the kidneys, but not the other organs, increased significantly with duration (Tandon et al. 1979).

Whole-body analysis of mice given a single intraperitoneal injection of 3.25 mg chromium(III)/kg as chromium trichloride showed that chromium trichloride was released very slowly over 21 days: 87% was retained 3 days after treatment, 73% after 7 days treatment, and 45% after 21 days. In contrast, mice given a single intraperitoneal injection of 3.23 chromium(VI)/kg as potassium dichromate retained only 31% of the chromium(VI) dose at 3 days, 16% at 7 days and 7.5% at 21 days. Mice injected weekly with

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chromium(III) compounds at 17% of the LD₅₀ retained 6 times the amount of chromium as mice injected with chromium(VI) compounds at 17% of the LD₅₀. The retention of chromium(III) was attributed to its ability to form coordination complexes with tissue components such as proteins and amino acids (Bryson and Goodall 1983).

In rats injected intraperitoneally with 2 mg chromium(VI)/kg/day as potassium chromate 6 days/week for 45 days, the mean levels of chromium (µg chromium/g wet weight) were 25.68 in the liver, 40.61 in the kidney, 7.56 in the heart, and 4.18 in the brain (Behari and Tandon 1980).

In rats injected subcutaneously with 5.25 mg chromium(VI)/kg as potassium dichromate, most of the chromium in the tissues analyzed was found in the red blood cells with a peak level (63 µg chromium/g) achieved 24 hours after dosing. White blood cells were not analyzed for chromium content. Whole plasma contained 2.7–35 µg/mL and the plasma ultrafiltrate contained 0.15–0.79 µg/mL. Tissue distribution 48 hours after dosing was as follows: 221.2 µg/g in renal cortex, 110.0 µg/g in liver, 103.0 µg/g in spleen, 86.8 µg/g in lung, 58.9 µg/g in renal medulla, and 8.8 µg/g in bone, compared with 2.28–5.98 µg/g in any tissues in controls. When rats were given repeated subcutaneous injections of 1.05 mg chromium(VI)/kg/day, every other day for 2, 4, 8, 10, or 12 weeks, most of the chromium was again found in the red blood cells. However, while red blood cell levels rose progressively during treatment, levels as high as those seen after a single dose were never achieved, even when the total dose exceeded the dose in the single injection experiment 10-fold. The tissue levels of chromium determined 48 hours after the last dose in the rats injected for 12 weeks were of the same order of magnitude as those seen after a single injection. These results suggest little tendency of soluble chromium(VI) compounds to accumulate in tissues with repeated exposure (Mutti et al. 1979).

In an *in vitro* study, whole blood samples were spiked with water-soluble chromium(VI) or chromium(III) compounds. The results showed a greater level of chromium inside erythrocytes after treatment with chromium(VI) compounds, compared to chromium(III) compounds. The investigators reported that only chromium(VI) compounds are taken up by erythrocytes and, presumably after reduction to chromium(III), form complexes with intracellular proteins that could not be eliminated (Lewalter et al. 1985).

The distribution of radioactivity was compared in mouse dams and fetuses following the intravenous injection of the dams with ⁵¹Chromium labelled-sodium dichromate(VI) or ⁵¹chromium labelled-chromium(III) trichloride. In the maternal tissues, the highest levels of radioactivity from both treatments were achieved in the renal cortex, but the concentration of radioactivity in the tissues of dams given the

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hexavalent form was much higher than that of the dams given the trivalent form. The patterns of distribution of radioactivity in other tissues were identical regardless of administered valence state, with the skeleton, liver, kidneys, and ovaries accumulating the highest levels and the brain and muscle accumulating the lowest levels. The serum concentration of radioactivity after treatment with chromium(III) was 3 times higher than that after treatment with chromium(VI). Radioactivity after treatment with both valence forms crossed the placenta, but the radioactivity from the hexavalent form crossed more readily. For chromium(VI), $\approx 12\%$ of the maternal serum concentration of radioactivity was found in the fetuses when the dams were administered sodium dichromate in mid-gestation (days 12–15). When the dams were injected in late gestation (days 16–18), $\approx 19\%$ of the radioactivity in maternal serum was found in the fetuses. For chromium(III), the fetal concentration of radioactivity was only $\approx 0.4\%$ of the maternal serum concentration when the dams were injected with radiolabeled chromium trichloride in mid-gestation and 0.8% of the maternal serum radioactivity concentration when injected in late gestation. Radioactivity from both treatments accumulated in fetal skeletons in calcified areas and in the yolk sac placenta (Danielsson et al. 1982). Danielsson et al. (1982) noted that the radioactivity after administration of chromium(VI) may represent chromium(III) after reduction in the tissues. Chromium(III) also crossed the placenta of mice injected intraperitoneally with chromium trichloride (Iijima et al. 1983). While the results indicate that both chromium(VI) and chromium(III) may pose developmental hazards, they cannot be used to indicate that exposure of pregnant animals to chromium(III) by inhalation or oral routes would result in significant placental transfer because chromium(III) compounds are not well absorbed by these routes (see Section 3.4.1).

Tissue distribution in rats and mice after 14 days of intraperitoneal injection of $0.8 \text{ mg chromium(VI)/day}$ as potassium chromate were: liver $6.00 \text{ } \mu\text{g/g}$ wet weight in rats and 8.89 in mice, kidney 24.14 and 11.77 , spleen 15.26 and 6.92 , femur 6.53 and 6.30 , lung 3.99 and 2.89 , heart 3.13 and 1.75 , muscle 1.10 and 0.51 , and blood 4.52 and 1.56 (Kargacin et al. 1993). Kidney and blood chromium concentrations were 2- and 4-fold higher, respectively, in rats compared to mice. Red blood cell concentrations were 3-fold higher in rats than mice and hemoglobin binding of chromium was twice as high in rats. By contrast, chromium levels in the blood were similar in rats and mice following oral exposure. The authors ascribed this to faster entry into the blood after intraperitoneal injection and thus a greater likelihood that chromium(VI) could be sequestered in rat erythrocytes by reduction.

3.4.3 Metabolism

Chromium(III) compounds are essential to normal glucose, protein, and fat metabolism. In addition, chromium(III) is capable of forming complexes with nucleic acids and proteins. Chromium(III) may also participate in intracellular reduction and oxidation reactions. Chromium(VI) is unstable inside the body and is ultimately reduced to chromium(III) *in vivo* by a variety of reducing agents. Chromium(V) and chromium(IV) are transient intermediates in this process.

Currently, the biological target for the essential effects of chromium(III) is unknown. Chromodulin, also referred to as GTF, has been proposed as one possible candidate (Jacquemet et al. 2003). The function of chromodulin, an oligopeptide complex containing four chromic ions, has not been established; however, a possible mechanism is that chromodulin facilitates the interaction of insulin with its cellular receptor sites, although this has not been proven (Anderson 1998a, 2003; IOM 2001).

In vivo and *in vitro* experiments in rats indicated that, in the lungs, chromium(VI) can be reduced to chromium(III) by ascorbate. The reduction of chromium(VI) by ascorbate results in a shorter residence time of chromium in the lungs and constitutes the first defense against oxidizing reagents in the lungs. When ascorbate is depleted from the lungs, chromium(VI) can also be reduced by glutathione. The level of ascorbic acid in the adult human lung has been estimated as approximately 7 mg/100 g wet tissue (Hornig 1975). The reduction of chromium(VI) by glutathione is slower and results in greater residence time of chromium in the lungs, compared to reduction by ascorbate (Suzuki and Fukuda 1990). Other studies reported the reduction of chromium(VI) to chromium(III) by epithelial lining fluid (ELF) obtained from the lungs of 15 individuals by bronchial lavage. The average reduction accounted for 0.6 µg chromium(VI)/mg of ELF protein. In addition, cell extracts made from pulmonary alveolar macrophages derived from five healthy male volunteers were able to reduce an average of 4.8 µg chromium(VI)/10⁶ cells or 14.4 µg chromium(VI)/mg protein (Petrilli et al. 1986b). Metabolism of the chromium(VI) to chromium(III) by these cell fractions significantly reduced the mutagenic potency of the chromium when tested in the Ames reversion assay. Postmitochondrial (S12) preparations of human lung cells (peripheral lung parenchyma and bronchial preparations) were also able to reduce chromium(VI) to chromium(III) (De Flora et al. 1984). Moreover, large individual differences were observed (De Flora et al. 1984, 1987b), and extracts from pulmonary alveolar macrophages of smokers reduced significantly more chromium(VI) to chromium(III) than extracts from cells of nonsmokers. Because chromium(III) does not readily enter cells, these data suggest that reduction of chromium(VI) by the ELF may constitute the first line of defense against toxicity of inhaled chromium compounds. Furthermore, uptake and reduction of

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chromium compounds by the pulmonary alveolar macrophages may constitute a second line of defense against pulmonary toxicity of chromium(VI) compounds. Microsomal reduction of chromium(VI) occurs in the lungs mainly as it does in the liver, as discussed below.

The first defense against chromium(VI) after oral exposure is the reduction of chromium(VI) to chromium(III) in the gastric environment where gastric juice (De Flora et al. 1987a) and ascorbate (Samitz 1970) play important roles. Studies using low-frequency electron paramagnetic resonance (EPR) spectrometry have shown that chromium(VI) is reduced to chromium(V) *in vivo* (Liu et al. 1994, 1995, 1997a, 1997b; Ueno et al. 1995b). *In vitro*, low concentrations of ascorbate favor the formation of chromium(V), whereas higher concentrations of ascorbate favor the formation of the reduced oxidation state, chromium(III) (Liu et al. 1995). EPR spectrometric monitoring also showed that chromium(VI) was rapidly reduced to chromium(V) on the skin of rats, with a 3-fold greater response when the stratum corneum was removed (Liu et al. 1997a). Thus, dermal effects from direct skin contact with chromium(VI) compounds may be mediated by rapid reduction to chromium(V). In whole blood and plasma, increasing ascorbate levels led to an increased oxidation of chromium(VI) to chromium(III) (Capellmann and Bolt 1992).

For humans, the overall chromium(VI)-reducing/sequestering capacities were estimated to be 0.7–2.1 mg/day for saliva, 8.3–12.5 mg/day for gastric juice, 11–24 mg for intestinal bacteria eliminated daily with feces, 3,300 mg/hour for liver, 234 mg/hour for males and 187 mg/hour for females for whole blood, 128 mg/hour for males and 93 mg/hour for females for red blood cells, 0.1–1.8 mg/hour for ELF, 136 mg/hour for pulmonary alveolar macrophages, and 260 mg/hour for peripheral lung parenchyma. Although these *ex vivo* data provide important information in the conversion of chromium(VI) to reduced states, the values may over- or underestimate the *in vivo* reducing capabilities (De Flora et al. 1997).

Reduction of chromium(VI) in the red blood cell occurs by the action of glutathione. Since the red blood cell membrane is permeable to chromium(VI) but not chromium(III), the chromium(III) formed by reduction of chromium(VI) by glutathione is essentially trapped within the erythrocyte for the life-span of the cell (Paustenbach et al. 2003), with approximately 1% of chromium eluting from the erythrocyte daily (ICSH 1980). Eventually, the diffusion of chromium(VI), the reduction to chromium(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane. Thus, there is a physiological drag so that increased diffusion results in greater chromium concentrations in the cell (Aaseth et al. 1982). It appears that the rate of uptake of chromium(VI) by red blood cells may not exceed the rate at which they

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reduce chromium(VI) to chromium(III) (Corbett et al. 1998). *In vitro* incubation of red blood cells with an excess of sodium chromate(VI) (10 mM) decreased glutathione levels to 10% of the original amount (Wiegand et al. 1984). The above concepts are applicable to the uptake and reduction of chromium(VI) in other cell types.

The effect of glutathione-depleting agents on the amounts of cellular chromium(III) and chromium(V) was determined in Chinese hamster V-79 cells treated with sodium chromate (Sugiyama and Tsuzuki 1994). Buthionine sulfoximine at 25 μ M reduced glutathione levels to about 1% of control values, and increased chromium(V) levels by about 67%. The total chromium uptake was decreased by about 20% and chromium(III) levels were decreased by 20%. Diethylmaleate (1 mM) decreased glutathione levels to <1%, decreased chromium(V) levels by 27% and chromium(III) levels by 31%. However, the cellular uptake of total chromium was decreased to nearly 46%. The authors explained that the reason that the diethylmaleate inhibited the reduction of chromium(VI) to both chromium(III) and chromium(V) was not due to the decreased uptake, but involved the inhibition of the chromate-reducing enzymes in the cell.

In addition to the reduction of chromium(VI) by ascorbate or glutathione, *in vitro* studies have demonstrated reduction of chromium(VI) by microsomal enzymes. Hepatic microsomal proteins from male Sprague-Dawley rats pretreated with chromium(VI) reduced chromium(VI) to chromium(III). The rate of reduction varied both with the concentration of microsomal protein and the concentration of nicotinamide adenine dinucleotide phosphate (NADPH). In the absence of NADPH, microsomes did not reduce significant amounts of chromium(VI) over the 24-hour observation period. Therefore, the reduction of chromium(VI) in rat hepatic microsomes is NADPH-dependent (Gruber and Jennette 1978). Another study followed the kinetics of chromium(VI) reduction in hepatic microsomes from rats (Garcia and Jennette 1981). Induction of cytochrome P448 enzymes had no effect on the kinetics of the reaction, while induction of cytochrome P450 and NADPH-cytochrome P450 reductase resulted in a decrease in the apparent chromate-enzyme dissociation constant, and an increase in the apparent second-order rate constant, and no change in the apparent turnover number. Inhibition of NADPH-cytochrome P450 reductase and NADH-cytochrome b_5 reductase inhibited the rate of microsomal reduction of chromium(VI), as did the addition of specific inhibitors of cytochrome P450. The results demonstrate the involvement of cytochrome P450, NADPH-dependent-cytochrome P450 reductase, and to a lesser extent cytochrome b_5 and NADH-dependent-cytochrome b_5 reductase, in the reduction of chromate by rat hepatic microsomes. The conversion of chromium(VI) to chromium(III) in rats can occur by electron transfer through cytochrome P450 and cytochrome b_5 . Both oxygen and carbon monoxide were found to inhibit the *in vitro* cytochrome P450 and cytochrome b_5 -dependent reduction of chromium(VI) (Mikalsen

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et al. 1989). The assertion that cytochrome P450 is involved in the reduction of chromium(VI) to chromium(III) has been further strengthened by Petrilli et al. (1985), who demonstrated that inducers of cytochrome P450 can increase the conversion of chromium(VI) to chromium(III) in S-9 mixtures prepared from the liver and lungs of exposed rats. Furthermore, it was observed that chromium(VI) can induce pulmonary cytochrome P450 and thus its own reduction in the lungs (Petrilli et al. 1985). Chromium(VI) apparently can alter the P450 activity in isolated rat microsomes. Witmer et al. (1994) demonstrated that hepatic microsomes from male rats treated with chromium(VI) resulted in a significant decrease in hydroxylation of testosterone at the 6 β , 16 α , and 2 α positions, indicating a decrease in the activity of P4503A1 and 3A2. In lung microsomes, an increased hydroxylation was observed at the 16 α and 16 β positions, indicating an increase in P450IIB1 activity. However, hepatic microsomes from treated females showed a 4-to 5-fold increase in hydroxylation activity of testosterone at the 6 β position, which demonstrated that the metabolic effects of chromium differ between males and females.

Two studies have examined possible species differences in the ability of microsomes to reduce chromium(VI) (Myers and Myers 1998; Pratt and Myers 1993). Chromium(VI) reduction was enzymatic and NADPH-dependent, and the rates were proportional to the amount of microsome added. In humans, the K_m for chromium(VI) was 1–3 orders of magnitude lower than K_m values in rats, although the V_{max} was similar. This suggests that the human liver has a much greater capacity to reduce chromium(VI) than the rat liver. Also contrary to the rodent data, oxygen and cytochrome P450 inhibitors (carbon monoxide, piperonyl butoxide, metyrapone, and aminopyrine) did not inhibit chromium(VI) reduction. These differences indicate that, in humans, cytochrome P450 does not play a significant role in the reduction process, but that other microsomal flavoproteins are responsible for reducing chromium(VI). Inhibition of flavoproteins by $TlCl_3$ decreased chromium(VI) reduction by 96–100%, while inhibition of cytochrome c reductase (P450 reductase) by bromo-4'-nitroacetophenone resulted in an 80–85% inhibition of chromium(VI) reduction. Combined, these observations implicate P450 reductase, working independently of cytochrome P450, as a major contributor in the reduction of chromium(VI) in human microsomes. These findings suggest that metabolism of chromium(VI) in rodent systems may not readily be extrapolated to humans.

Microsomal reduction of chromium(VI) can also result in the formation of chromium(V), which involves a one-electron transfer from the microsomal electron-transport cytochrome P450 system in rats. The chromium(V) complexes are characterized as labile and reactive. These chromium(V) intermediates persist for 1 hour *in vitro*, making them likely to interact with deoxyribonucleic acid (DNA), which may eventually lead to cancer (Jennette 1982). Because chromium(V) complexes are labile and reactive,

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detection of chromium(V) after *in vivo* exposure to chromium(VI) was difficult in the past. More recently, Liu et al. (1994) have demonstrated that chromium(V) is formed *in vivo* by using low-frequency electron paramagnetic resonance (EPR) spectroscopy on whole mice. In mice injected with sodium dichromate(VI) intravenously into the tail vein, maximum levels of chromium(V) were detected within 10 minutes and declined slowly with a life-time of about 37 minutes. The time to reach peak *in vivo* levels of chromium(V) decreased, in a linear manner as the administered dose levels of sodium dichromate decreased. The relative tissue distributions of chromium(V) indicated that most was found in the liver and much lesser amounts in blood. None was detected in kidney, spleen, heart, or lung. When the mice were pretreated with metal ion chelators, the intensity of the EPR signal decreased demonstrating that the formation of chromium(V) was inhibited. Reactions of chromium(VI) with glutathione produced two chromium(V) complexes and a glutathione thiyl radical. Reactions of chromium(VI) with DNA in the presence of glutathione produced chromium-DNA adducts. The level of chromium-DNA adduct formation correlated with chromium(V) formation. The reaction of chromium(VI) with hydrogen peroxide produced hydroxyl radicals. Reactions of chromium(VI) with DNA in the presence of high concentrations of hydrogen peroxide (millimolar compared to 10^{-7} – 10^{-9} M inside cells) produced significant DNA strand breakage and the 8-hydroxy guanosine adduct, which correlated with hydroxyl radical production (Aiyar et al. 1989, 1991). Very little chromium(V) was generated by this pathway. It was postulated that the reaction of chromium(VI) with hydrogen peroxide produces tetraperoxochromium(V) species that act as a catalyst in a Fenton-type reaction producing hydroxyl radicals in which chromium(V) is continuously being recycled back to chromium(VI). The regeneration of chromium(VI) through interactions with chromium(V) and hydrogen peroxide is consistent with the findings of Molyneux and Davies (1995) (see Section 3.5.2). As discussed above, chromium(VI) is ultimately reduced to chromium(III) within the cell. Chromium(III) can form stable complexes with DNA and protein (De Flora and Wetterhahn 1989), which is discussed further in Section 3.5.2.

The mechanism for clearance of chromium(VI) once reduced inside the liver cell may involve a chromium(III)-glutathione complex. The glutathione complex would be soluble through the cell membrane and capable of entering the bile (Norseth et al. 1982). The complexing of chromium(III) to other ligands has been shown to make them more permeable to the cell membrane (Warren et al. 1981).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Normal urinary levels of chromium in humans have been reported to range from 0.22 to 1.8 µg/L (0.00024–0.0018 mg/L) with a median level of 0.4 µg/L (0.0004 mg/L) (IOM 2001; Iyengar and Woittiez 1988). Humans exposed to 0.05–1.7 mg chromium(III)/m³ as chromium sulfate and 0.01–0.1 mg chromium(VI)/m³ as potassium dichromate (8-hour TWA) had urinary excretion levels of 0.0247–0.037 mg chromium(III)/L. Workers exposed mainly to chromium(VI) compounds had higher urinary chromium levels than workers exposed primarily to chromium(III) compounds. An analysis of the urine did not detect the hexavalent form of chromium, indicating that chromium(VI) was rapidly reduced before excretion (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Chromium(III) compounds were excreted rapidly in the urine of workers, following inhalation exposure to chromium(III) as chromium lignosulfonate. Workers exposed to 0.005–0.23 mg chromium(III)/m³ had urine concentrations of 0.011–0.017 mg chromium(III)/L. The half-time for urinary excretion of chromium was short, 4–10 hours, based on an open, one-compartment kinetic model (Kiilunen et al. 1983). Tannery workers had higher urinary chromium(III) concentrations in postshift urine samples taken Friday afternoon and in preshift urine samples taken Monday, compared to controls. These workers also had hair concentrations of chromium that correlated with urinary levels. Analysis of workroom air revealed no detectable chromium(VI) and 0.0017 mg chromium(III)/m³ (time-weighted average) (Randall and Gibson 1987). Elimination of chromium(III) from hair, serum, and urine has been studied in a group of 5 men who had ceased working in a leather tannery 9 months earlier (Simpson and Gibson 1992). Compared to levels recorded during employment, the mean level of chromium in hair was reduced from 28.5 to 2.9 µmol/g; serum levels were reduced from 9.4 to 3.8 nmol/L. These levels are comparable to those in the general population. Urine levels were unchanged (13.8 nmol/L while working and 14.4 nmol/L 9 months later); the authors stated that this was probably caused by consumption of beer (a source of chromium) the night before sampling. Data from autopsy studies indicate that chromium can be retained in the lung for decades following cessation of occupational exposures (Brune et al. 1980; Hyodo et al. 1980; Mancuso 1997b).

Peak urinary chromium concentrations were observed at 6 hours (the first time point examined) in rats exposed intratracheally to 0.44 mg/kg chromium(III) as chromium acetate hydroxide or chromium(VI) as sodium dichromate (Gao et al. 1993). Chromium urinary concentrations decreased rapidly, falling from 4,535 µg chromium/g creatinine at 6 hours to 148 µg chromium/g at 72 hours for the chromium acetate

hydroxide and from 2,947 µg chromium/g creatinine at 6 hours to 339 µg chromium/g at 72 hours for sodium dichromate.

Elimination of chromium was very slow in rats exposed to 2.1 mg chromium(VI)/m³ as zinc chromate 6 hours/day for 4 days. Urinary levels of chromium remained almost constant for 4 days after exposure and then decreased, indicating that chromium bound inside the erythrocyte is released slowly (Langård et al. 1978).

3.4.4.2 Oral Exposure

Given the low absorption of chromium compounds by the oral route, the major pathway of excretion after oral exposure is through the feces.

An acute, oral dose of radioactive chromium(III) as chromium chloride or chromium(VI) as sodium chromate was administered to humans after which feces and urine were collected for 24 hours and 6 days, respectively, and analyzed for chromium. The amount of chromium in the 6-day fecal collection was 99.6 and 89.4% of the dose for chromium(III) and chromium(VI) compounds, respectively. The amount of chromium in the 24-hour urine collection was 0.5 and 2.1% of the dose for chromium(III) and chromium(VI) compounds, respectively (Donaldson and Barreras 1966). In subjects drinking 0.001–0.1 mg chromium(VI)/kg/day as potassium chromate in water for 3 days, <2–8% of the dose was excreted in the urine (Finley et al. 1997). The percentage of the dose excreted appeared to increase with increasing dose.

Urinary excretion rates have been measured in humans after oral exposure to several chromium compounds (Finley et al. 1996b). A group of four male and two female volunteers ingested capsules containing chromium(III) picolinate at a dose of 200 µg/day for 7 days, to ensure that chromium deficiency was not a confounding factor. They then ingested 0.005 mg/kg/day chromium(VI) as potassium chromate (3 days), and 1.0 mg/kg/day chromium(III) as chromic oxide (3 days), with 3 days without dosing between the potassium chromate and chromic oxide doses. Urinary excretion rates of chromium were significantly elevated compared to postdosing control levels after seven daily doses of chromium(III) picolinate (2.4±0.8 versus 0.75±0.53 µg/day). The excretion rate increased sharply on the first of 3 days of potassium chromate dosing (11±17 µg/day) and remained steady over the next 2 days (13–14 µg/day). Excretion rates fell to 2.5±0.72 during 2 days without dosing and continued to fall during the 3 days of chromic oxide dosing, reaching rates similar to those seen postdosing. Mean pooled

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urinary concentrations during the dosing periods were 2.4 µg chromium/g creatinine from exposure to chromium(VI) and 0.4 µg chromium/g creatinine from exposure to chromium(III) as compared to 0.23 µg chromium/g creatinine during the postdosing time periods. The lower urinary excretion of chromium(III) after exposure to chromic oxide reflects the poorer absorption of inorganic chromium(III) compounds compared to inorganic chromium(VI) compounds.

The half-life for chromium urinary excretion after administration in drinking water as potassium dichromate has been estimated in humans (Kerger et al. 1997). Ingestion of 0.05 mg chromium(VI)/kg resulted in an extended time course of excretion. Approximately 76–82% of the 14-day total amount of chromium in the urine was excreted within the first 4 days (mean peak concentration 209 µg chromium/g creatinine; range 29–585 µg chromium/g creatinine). The average urinary excretion half-life for four of the volunteers was 39 hours at this dose. All subjects had returned to background concentrations (0.5–2.0 µg chromium/g creatinine) by 14 days postdosing. About 87% of the total amount of chromium in the urine measured over 8 days was excreted during the first 4 days for one volunteer ingesting 0.03 mg chromium(VI)/kg (peak 97 µg chromium/g creatinine on day of ingestion). Urinary chromium concentrations had returned to an average of 2.5 µg chromium/g creatinine within 7 days postdosing, the last time point measured. Urinary excretion half-life in this volunteer was 37 hours. Similar time courses of excretion were observed when volunteers took the same doses as daily doses over 3-day periods. An earlier study by this group (Kerger et al. 1996a) examined urinary excretion half-lives following a bolus dose of 10 ppm (approximately 0.06 mg chromium/kg) chromium(III) chloride, potassium dichromate reduced with orange juice (presumably, the juice reduced the potassium dichromate to chromium(III)-organic complexes and chromium(III) ions), or potassium dichromate. The calculated urinary excretion half-lives for the three chromium solutions were 10.3, 15, and 39.3 hours, respectively. The potassium dichromate half-life is consistent with the results from the Kerger et al. (1997) study. If, in these studies, all of the absorbed chromium(VI) was rapidly and completely converted to chromium(III), there should be no difference in urinary half-life. The difference in excretion half-lives following dosing with chromium(III) and chromium(VI) appears to reflect incomplete reduction of absorbed chromium(VI) to chromium(III) as well as longer retention of chromium(VI) in tissues. The prolonged half-life following dosing with chromium(VI) appears to be a composite of the half-lives the chromium(VI) and chromium(III) derived from the reduction of chromium(VI) in the blood. Given that most is converted to chromium(III), the half-life for the sequestered chromium is quite long (much longer than 40 hours) and reflects the half-life of chromium observed in the red blood cells. Pretreatment of chromium(VI) with orange juice apparently did not convert all chromium(VI) to chromium(III), as indicated by a half-life of 15 hours.

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The urinary excretion kinetics of chromium have also been examined in eight adults that were administered chromium(III) at 400 µg/day as chromium(III) picolinate for 3 consecutive days (Gargas et al. 1994). The mean time to peak urinary concentration was 7.18 ± 2.11 hours (range 2.9–13.0 hours), the mean peak concentration being 7.92 ± 4.24 µg chromium/g creatinine (range 3.58–19.13 µg/g creatinine). Excretion diminished rapidly after the peak, but did not appear to return to background in most of the volunteers before the next daily dose.

Pharmacokinetic models were used to predict the retention and excretion of ingested chromium(III) picolinate (Stearns et al. 1995a). A single dose of 5.01 mg (assuming 2.8% or 140 µg of the chromium(III) picolinate is absorbed) resulted in 11 µg (7.9%) retained after 1 year. The model predicted that about 1.4 µg would still be present in body tissues 10 years after dosing, and continuous dosing over a 1-year period would result in 6.2 mg of chromium(III) picolinate being retained, requiring about 20 years to reduce the retained level to 0.046 mg. These projected retention estimates may be 2–4-fold lower than results obtained from actual clinical findings. The authors caution that accumulative daily intake of chromium(III) may result in tissue concentrations that could be genotoxic.

Daily urinary excretion levels of chromium were nearly identical in men and women (averages of 0.17 and 0.20 µg/L, respectively; 0.18 µg/L combined) who ate normal dietary levels of chromium (≈ 60 µg chromium(III)/day). When the subjects' normal diets were supplemented with 200 µg chromium(III)/day as chromium trichloride to provide intakes of ≈ 260 µg chromium(III)/day, urinary excretion of chromium rose proportionately to an average of 0.98 µg/L combined. Thus a 5-fold increase in oral intake resulted in about a five-fold increase in excretion, indicating absorption was proportional to the dose regardless of whether the source was food or supplement (Anderson et al. 1983). A group of 23 elderly subjects who received an average of 24.5 µg/day (0.00035 mg chromium(III)/kg/day) from their normal diets excreted 0.4 µg chromium/day in the urine (1.6%) and 23.9 µg chromium/day in the feces (97.6%), with a net retention of 0.2 µg/day (0.8%). Based on the 1980 daily requirement for absorbable chromium of 1 µg/day by the National Academy of Science Food and Nutrition Board, the retention was considered adequate for their requirements (Bunker et al. 1984).

An estimate of the half-life of elimination from plasma has been reported in humans. Uptake of potassium dichromate was determined in a man who was given 0.8 mg of chromium(VI) in drinking water 5 times each day for 17 days (Paustenbach et al. 1996). Steady-state concentrations of chromium in blood were attained after 7 days and a plasma elimination half-life of 36 hours was estimated.

Measurement of the chromium content in 255 milk samples from 45 lactating American women revealed that most samples contained $<0.4 \mu\text{g/L}$ with a mean value of $0.3 \mu\text{g/L}$ (Casey and Hambidge 1984). Another study (Anderson et al. 1993) measured chromium levels in the breast milk of 17 women 60 days postpartum, and reported mean levels of $\sim 0.2 \mu\text{g/L}$. Lactation, therefore, represents a route of excretion of chromium and a potential route of exposure to the nursing infant. However, the precise relationship between maternal chromium levels and levels in breast milk is unclear, if such a relationship exists at all (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Chromium can be excreted in hair and fingernails. Mean trace levels of chromium detected in the hair of individuals from the general population of several countries were as follows: United States, 0.23 ppm; Canada, 0.35 ppm; Poland, 0.27 ppm; Japan, 0.23 ppm; and India, 1.02 ppm (Takagi et al. 1986). Mean levels of chromium in the fingernails of these populations were: United States, 0.52 ppm; Canada, 0.82 ppm; Poland, 0.52 ppm; Japan, 1.4 ppm; and India, 1.3 ppm (Takagi et al. 1988).

Rats given 18 mg chromium(VI)/kg as potassium dichromate by gavage excreted about 25 μg chromium in the first 24 hours after dosing and $\approx 10 \mu\text{g}$ chromium in each of the next 24-hour periods (Banner et al. 1986).

In rats and hamsters fed chromium compounds, fecal excretion of chromium varied slightly from 97 to 99% of the administered dose. Urinary excretion of chromium varied from 0.6 to 1.4% of the dose administered as either chromium(III) or chromium(VI) compounds (Donaldson and Barreras 1966; Henderson et al. 1979; Sayato et al. 1980). The urinary and fecal excretion over 2-day periods in rats treated for 8 days by gavage with 13.92 mg chromium/kg/day in corn oil was higher when soil containing 70% chromium(III) and 30% chromium(VI) was the source of chromium than when chromium(VI) as calcium chromate was the source (see Section 3.4.2.2). Total urinary and fecal excretion of chromium on days 1 and 2 of dosing were 1.8 and 19%, respectively, of the dose from soil and <0.5 and 1.8%, respectively, of the dose from calcium chromate. Total urinary and fecal excretion of chromium on days 7 and 8 of dosing were higher than on days 1 and 2. For contaminated soil, urinary excretion was 1.12% and fecal excretion was 40.6% of the dose. For calcium chromate, urinary excretion was 0.21% and fecal excretion was 12.35% of the dose (Witmer et al. 1991). Whether the higher excretion of chromium after dosing with soil than with the chromate salt represents greater bioavailability from soil could not be determined because about 50% of the administered dose could not be accounted for from the excretion and distribution data (see Section 3.4.2.2). Excretion of chromium(III) in dogs was approximately equal

to the clearance of creatinine, indicating little tubular absorption or reabsorption of chromium in the kidneys (Donaldson et al. 1984).

3.4.4.3 Dermal Exposure

Information regarding the excretion of chromium in humans after dermal exposure to chromium or its compounds is limited. Fourteen days after application of a salve containing potassium chromate(VI), which resulted in skin necrosis and sloughing at the application site, chromium was found at 8 mg/L in the urine and 0.61 mg/100 g in the feces of one individual (Brieger 1920). A slight increase (over background levels) in urinary chromium levels was observed in four subjects submersed in a tub of chlorinated water containing 22 mg chromium(VI)/L as potassium dichromate(VI) for 3 hours (Corbett et al. 1997). For three of the four subjects, the increase in urinary chromium excretion was <1 µg/day over the 5-day collection period.

⁵¹Chromium was detected in the urine of guinea pigs after radiolabeled sodium chromate(VI) or chromium(III) trichloride solutions were placed over skin depots that were monitored by scintillation counting to determine the dermal absorption (Wahlberg and Skog 1965).

3.4.4.4 Other Routes of Exposure

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Michel et al. 1987; Sunderman et al. 1989). Whether corrosion or wear of the implant can release chromium (or other metal components) into the systemic circulation depends on the nature of the device. In one study, the mean postoperative blood and urine levels of chromium of nine patients with total hip replacements made from a cast cobalt-chromium-molybdenum alloy were 3.9 and 6.2 µg/L, respectively, compared with preoperative blood and urine levels of 1.4 and 0.4 µg/L, respectively. High blood and urinary levels of chromium persisted when measured at intervals over a year or more after surgery. These data suggest significant wear or corrosion of the metal components. No significant difference was found for patients with hip replacements made from the alloy and articulated with polyethylene (Coleman et al. 1973). Similarly, serum and urinary levels of chromium in patients with implants made from a porous coated cobalt chromium alloy with polyethylene components (to prevent metal-to-metal contact) were not significantly different from patients with implants made without chromium (Sunderman et al. 1989).

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A number of factors have been shown to alter the rate of excretion of chromium in humans. Intravenous injection of calcium EDTA resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Both acute and chronic exercises have been shown to increase chromium excretion in the urine, though the increased excretion did not appear to be accompanied with decreased levels of total native chromium (Rubin et al. 1998). An increased rate of chromium excretion has been reported in women in the first 26 weeks of pregnancy (Morris et al. 1995b). Chromium supplementation did not appear to alter the rate of excretion into breast milk in postpartum women (Mohamedshah et al. 1998).

The urinary excretion of chromium after a single or during repeated subcutaneous injections of potassium dichromate was followed in rats. Following a single dose of 5.35 mg chromium(VI)/kg, chromium was excreted rapidly in two phases and was essentially complete at 48 hours. The filtered chromium load rose considerably during the first few hours after dosing and exceeded the tubular reabsorption rate. This increase was followed by a decrease that paralleled the urinary excretion of chromium. During repeated injections with 1.05 mg chromium(VI)/kg/day, every other day for 12 weeks, urinary excretion and diffusible chromium renal clearance rose at relatively high parallel rates, and reached plateaus at 10 ng/min for urinary excretion and 550 μ L/minute for renal clearance. The filtered load increased slightly. Since high levels of chromium were found in the renal cortex (see Section 3.4.2.4), the tubular reabsorption appeared to be limited by the accumulation of chromium in the tubular epithelium (Mutti et al. 1979).

Rats given a subcutaneous injection of potassium dichromate (chromium(VI)) and chromium nitrate (chromium(III)) excreted 36% of the chromium(VI) dose in urine and 13.9% in the feces within 7 days; 8 and 24.2% of the chromium(III) was excreted in the urine and feces within the same time period, respectively (Yamaguchi et al. 1983). Within 4 days after an intravenous dose of 51 chromium as chromium(III) chloride at 3 mg/kg chromium, rats excreted 5.23% of the dose in the feces and 16.3% in the urine (Gregus and Klaassen 1986).

In rats treated by intravenous injection with 51 chromium-labeled sodium chromate (chromium(VI)) or chromium(III) trichloride at 0.0003 or 0.345 mg chromium/kg, the bile contained 2–2.5% of the dose following chromium(VI) exposure; however, after chromium(III) exposure the concentration in the bile was \approx 50 times lower (Manzo et al. 1983). Similarly, 3.5–8.4% of chromium(VI) compounds was excreted in the bile as chromium(III), compared to 0.1–0.5% of chromium(III) compounds, after intravenous injection in rats (Cikrt and Bencko 1979; Norseth et al. 1982). Administration of

diethylmaleate, which depletes glutathione, resulted in only chromium(VI) in the bile after injection of sodium chromate.

Two hours after dosing rats intravenously with potassium dichromate at 0.45–4.5 mg chromium(VI)/kg, 1.4–2.2% of the chromium was recovered in the bile. Less than 1% of the total measurable chromium in the bile was identified as chromium(VI) compounds (Cavalleri et al. 1985).

Male Swiss mice exposed to 52 mg chromium(III)/kg as chromium chloride by single intraperitoneal injection or subcutaneous injection had plasma clearance half-times of 41.2 and 30.6 hours, respectively. In each case, blood levels reached control levels by 6–10 days (Sipowicz et al. 1997).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of

toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

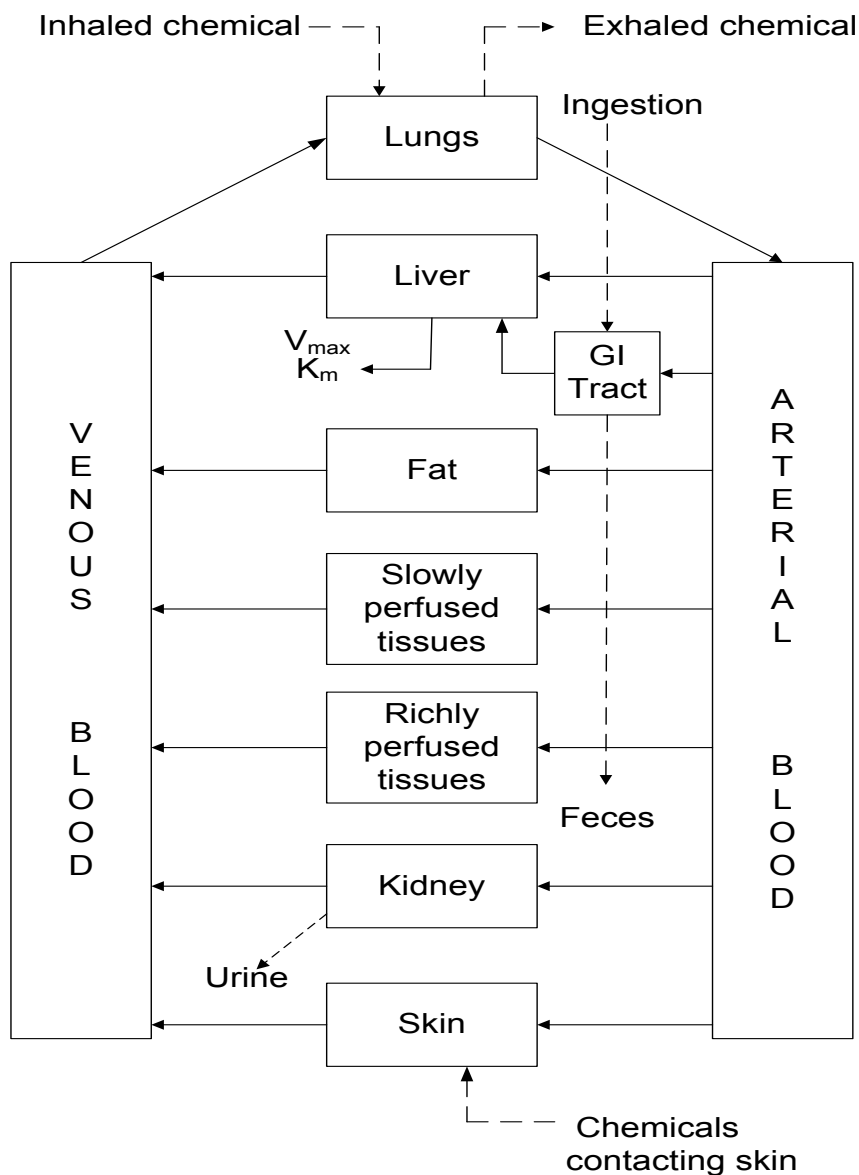
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. [Figure 3-5](#) shows a conceptualized representation of a PBPK model.

PBPK models for chromium are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. Two PBPK models for chromium have been reported that simulated developed by O'Flaherty absorption, distribution, metabolism, elimination, and excretion of chromium(III) and chromium(VI) compounds in the rat (O'Flaherty 1993c, 1996) and human (O'Flaherty et al. 2001).

3.4.5.1 O'Flaherty Model (1993a, 1996, 2001)

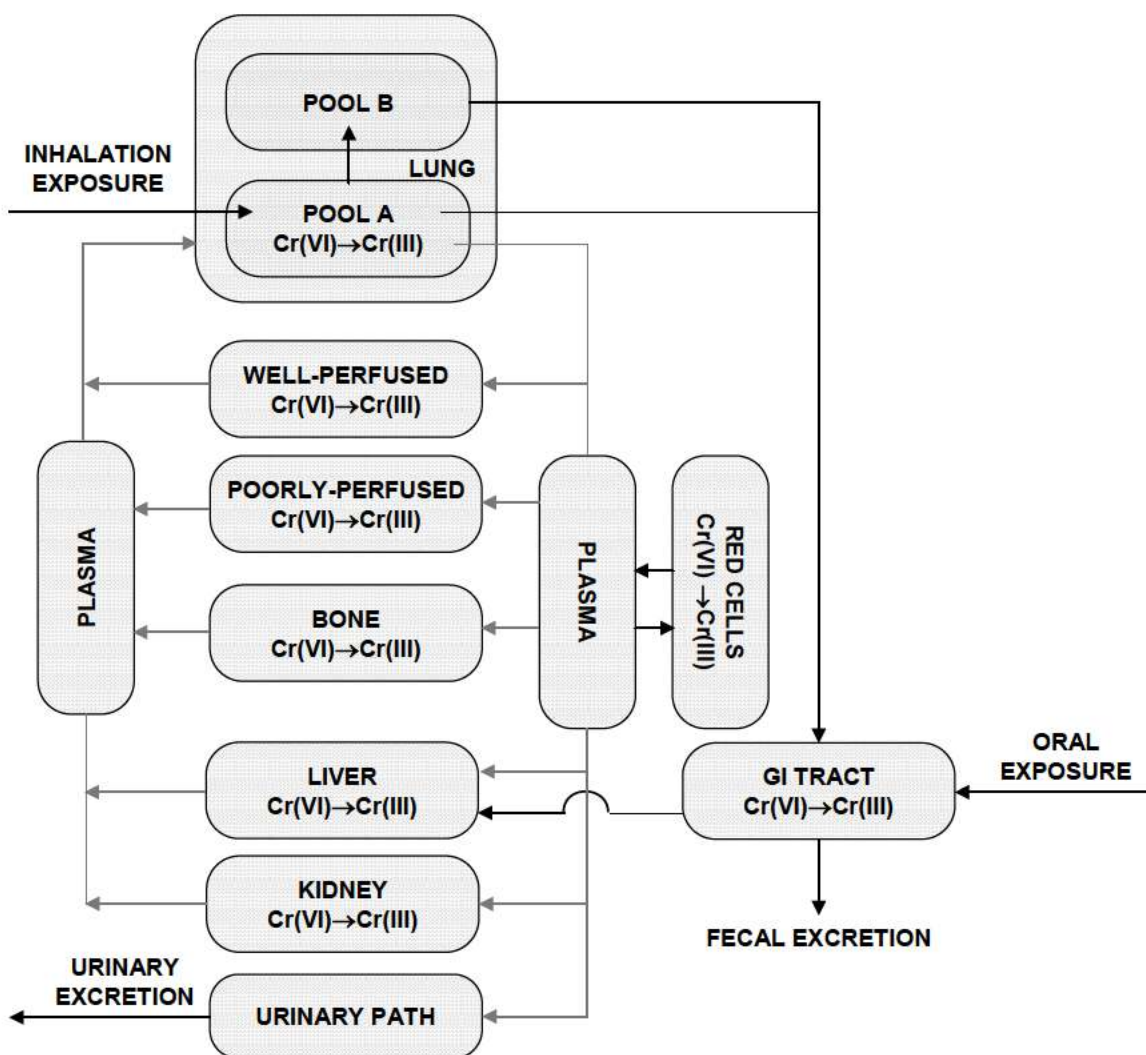
The structure of the O'Flaherty model is depicted in [Figure 3-6](#). Values for chromium parameters in the rat and human model are presented in [Table 3-11](#). The model includes compartments representing bone, kidney, liver, gastrointestinal tract, plasma, poorly-perfused tissues (e.g., muscle, skin), red blood cells, respiratory tract, and well-perfused tissues (e.g., brain, heart, lung, viscera). Chromium(VI) is assumed to

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Figure 3-6. A Physiologically Based Model of Chromium Kinetics in the Rat

Source: O'Flaherty et al. 1996

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Table 3-11. Chemical-specific Parameters in the Rat and Human Chromium Models

	Rat		Human		
Parameter ^a	Cr(III)	Cr(VI)	Cr(III)	Cr(VI)	Definition
Absorption					
KGI	0.01	0.04	0.25	2.5	First-order rate constant for absorption from the gastrointestinal tract (Da ⁻¹)
KLU	0.2	2.0	NA	NA	First-order rate constant for absorption from the bioavailable lung pool (pool A) (Da ⁻¹)
KMUCOA	0.8	0.8	NA	NA	First-order rate constant for mucociliary clearance from pool A to the gastrointestinal tract (Da ⁻¹)
KMUCOB	0.025	0.025	NA	NA	First-order rate constant for mucociliary clearance from the nonbioavailable lung pool (pool B) to the gastrointestinal tract (Da ⁻¹)
KLUAB	1.2	1.2	NA	NA	First-order rate constant for transfer from pool A to pool B (Da ⁻¹)
FRLUNG	NA	NA	0.3	0.3	Fraction of inhaled chromium absorbed to blood
FRTRGI	NA	NA	0.7	0.7	Fraction of inhaled chromium transferred to gastrointestinal tract.
Distribution					
CR	5.0	15.0	NA ^b	NA ^b	Relative clearance of chromium into mineralizing bone (liters of blood plasma cleared per liter of new bone formed)
KINRBC	0.0003	1.5	12.0	NA	Clearance from plasma to red cell (L/Da)
KDIN	0.007	1.5	3.0	30.0	Clearance from plasma to kidney (L/Da)
LDIN	0.0001	1.5	3.0	30.0	Clearance from plasma to liver (L/Da)
WDIN	0.0001	1.5	3.0	30.0	Clearance from plasma to other well-perfused tissues (L/Da)
PDIN	0.0001	0.01	3.0	30.0	Clearance from plasma to poorly-perfused tissues (L/Da)
BDIN	0.0001	0.01	NA ^b	NA ^b	Clearance from plasma to bone (L/Da)
CR	NA	NA	5.0	15.0	Fraction deposition from blood to forming bone
KOUTRBC	0.0003	10.0	12.0	NA	Clearance from red cell to plasma (L/Da)
KDOUT	0.001	10.0	3.0	30.0	Clearance from kidney to plasma (L/Da)
LDOUT	0.0003	10.0	3.0	30.0	Clearance from liver to plasma (L/Da)
WDOUT	0.001	10.0	3.0	30.0	Clearance from other well-perfused tissues to plasma (L/Da)
PDOUT	0.003	10.0	3.0	30.0	Clearance from poorly perfused tissues to plasma (L/Da)
BDOUT	0.003	10.0	NA ^b	NA ^b	Clearance from bone to plasma (L/Da)
Excretion					
KFX	1.5	1.5	14.0	14.0	First-order rate constant for loss of chromium from intestinal tract contents to the feces (Da ⁻¹)

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Table 3-11. Chemical-specific Parameters in the Rat and Human Chromium Models

Parameter ^a	Rat		Human		Definition
	Cr(III)	Cr(VI)	Cr(III)	Cr(VI)	
QEC	0.065	0.065	NA ^c	NA ^c	Excretion clearance from the plasma (urinary clearance) (L/kg/Da)
CLEAR ^b	NA	NA	12.0	12.0	Parameter in expression for clearance from blood plasma to urine (L/day)
MAX ^b	NA	NA	0.008	0.008	Parameter in expression for clearance from blood plasma to urine (mg/day)
KM ^b	NA	NA	0.0008	0.0008	Parameter in expression for clearance from blood plasma to urine (mg/L)
FB	0.0	0.0	NA	NA	Fraction of body burden secreted in the bile
FI	0.0	0.0	NA	NA	Fraction of body burden excreted via the gastrointestinal tract
Reduction					
KREDRC	NA	0.7	NA	7.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in the red cell (Da ⁻¹)
KREDBP	NA	NA	NA	0.2	First-order rate constant for reduction of Cr(VI) to Cr(III) in blood plasma (Da ⁻¹)
KREDKL	NA	NA	NA	500.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in kidney (Da ⁻¹)
KREDGI	NA	10.0	NA	100.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in gastrointestinal tract contents (Da ⁻¹)
KRED	NA	0.5	NA	5.0	First-order rate constant for reduction of Cr(VI) to Cr(III) in all other tissues and in lung contents (Da ⁻¹)
Lag time for excretion of urine					
FRHOLD	0.7	0.7	NA	NA	Fraction of urinary chromium not excreted immediately; that is, temporarily held in pool
KHOLD	0.05	0.05	NA	NA	First-order rate constant for excretion from the retained urine pool (Da ⁻¹)
FR	0.10	0.10	NA	NA	Fraction of chromium in retained urine that is associated with the kidney

^aParameter names are those for human model in cases where the reported rat and human parameter names were not identical.

^bExchanges between blood plasma and cortical and trabecular bone are simulated as functions of bone formation and resorption rates.

^c $QE = CLEAR - \frac{MAX}{KM + CBP}$, where QE is clearance from blood plasma to urine (L/day) and CBP is plasma concentration of chromium (mg/L).

NA = not applicable

Sources: O'Flaherty 1996 (rat parameters); O'Flaherty et al. 2001 (human parameters)

be reduced to chromium(III) in all tissues, and in the gastrointestinal and respiratory tract. Reduction is represented as a first-order rate, with distinct rates for the red cell and gastrointestinal tract, and a single value representing all other tissues.

Absorption of chromium from the gastrointestinal tract is simulated as the sum of competing first-order processes; transfer to the liver (absorption) and transfer of unabsorbed chromium to feces. Parameter values for these two processes result in absorption of approximately 1–2% of an oral dose.

The respiratory tract is represented with two subcompartments to distinguish a bioavailable chromium (pool A) from a nonbioavailable chromium (pool B). Inhaled chromium first deposits in pool A from where it can be transferred to blood (i.e., absorption), transferred to the gastrointestinal tract (i.e., mucocilliary clearance), or transferred to pool B. Chromium in pool B is cleared to the gastrointestinal tract. Transfers within and out of the respiratory tract are represented with first-order rate constants.

Transfers of chromium between plasma and soft tissues are represented with clearance terms (i.e., L/day), where clearance is given by the first-order rate constant (k_e) for transfer and tissue volume (V , $\text{clearance} = k_e \times V$). Distinct plasma-to-tissue and tissue-to-plasma clearance values are assigned to chromium(III) and chromium(VI), with faster clearances assumed for chromium(VI), by a factor of 3,000–10,000, compared to chromium(III). In the rat model, transfers of chromium between plasma and bone are represented with clearance constants; however, this is expanded in the human model to represent chromium uptake into bone as a function of bone formation rate, and return of chromium to plasma from bone as a function of bone resorption rate (see also O’Flaherty 1993c, 1995 for further information on the bone growth and reabsorption model).

Absorbed chromium is excreted in urine. Although a biliary secretion pathway was included in the model, flux through the pathway was subsequently set to zero, based on optimizations of the model against observations. This parameterization is equivalent to assuming that either chromium is not secreted in bile, or if it is secreted into bile, it is essentially completely (and rapidly) absorbed. Urinary excretion of chromium is represented as clearance from plasma. In the rat model, plasma-to-urine clearance was assigned a constant value. In the human model, urinary clearance is represented as a variable fraction of the glomerular filtration rate, with the fraction increasing with increasing plasma concentration (e.g., 0.7% of GFR at a concentration of 0.0001 mg/L; 40% of GFR at 0.01 mg/L).

Validation of the model. Optimization of parameter values and evaluation of the rat model are described in O'Flaherty (1996). Initial values for the rat model were established based on data reported in various intravenous, oral, or intratracheal rat studies (Bragt and van Dura 1983; Cavalleri et al. 1985; Cikrt and Bencko 1979; Edel and Sabbioni 1985; MacKenzie et al. 1959; Mertz et al. 1969; Thompson and Hollis 1958; Weber 1983). Parameter values were optimized against data on kinetics of tissue levels and chromium excretion measured in rats that received intratracheal doses of $^{51}\text{Cr(VI)}$ or $^{51}\text{Cr(III)}$ (Bragt and van Dura 1983; Edel and Sabbioni 1985; Weber 1983). The optimized rat model was evaluated by comparing predictions of blood ^{51}Cr kinetics to observations made in rats exposed 6 hours/day for 4 days to dusts of zinc ^{51}Cr chromate (76% respirable, Langård et al. 1978). Predicted blood concentrations during exposure and postexposure kinetics agreed with observations. The model was also evaluated against data from a drinking water study in which rats were exposed to drinking water concentrations of $\text{K}_2\text{Cr(VI)O}_4$ ranging from 0.45 to 25 mg/L, or to Cr(III)Cl_3 at a concentration of 25 mg/L for a period of 1 year (MacKenzie et al. 1958). This was not a completely independent evaluation of the model since data from this study were used to set parameters for fractional uptake of chromium into bone. Ranges for predicted:observed ratios for terminal tissue levels in rats exposed to 0.45–25 mg chromium(VI)/L were 1.2–5 for liver, 0.3–1.2 for kidney, and 0.2–1.5 for bone (femur). The ratio for rats exposed to 25 mg chromium(III)/L were 15 for liver, 0.9 for kidney, and 2 for bone.

Optimization and evaluation of the human model is described in O'Flaherty et al. (2001). The model was optimized with data on plasma and red blood cell chromium concentrations, and urinary chromium excretion in adult subjects who ingested a single dose of chromium(III) as CrCl_3 or chromium(VI) as $\text{K}_2\text{Cr}_2\text{O}_7$ (Finley et al. 1997; Kerger et al. 1996a, see Section 3.4.1.2 for description of these studies). The model was evaluated against data on plasma chromium concentration kinetics and urinary excretion of chromium in a single adult subject who ingested 4 mg chromium(VI)/day as $\text{K}_2\text{Cr}_2\text{O}_7$ for 17 days (Paustenbach et al. 1996; see Section 3.4.1.2), with the only adjusted parameter being the absorption rate constant. Although the model was optimized based on data from single dose studies, it reproduced the observed steady-state plasma chromium concentration, time to steady state, and elimination kinetics following cessation of the 17-day exposure.

Risk assessment. The model accounts for most of the major features of chromium(VI) and chromium(III) absorption and kinetics, and reduction chromium(VI) to chromium(III), uptake into and retention in red blood cells, and uptake and retention in bone. The human model associated bone chromium kinetics with bone formation and resorption and provides a structure for simulating age-dependent kinetics attributable to changes in bone turnover (e.g., growth, pregnancy, senescence).

Bioavailability of chromium from environmental sources is mostly unknown, except for a few chemically defined salts.

Target tissues. The rat and human models include parameters for predicting levels of chromium(III) and chromium(VI) in plasma, red blood cells, kidney, liver, bone, gastrointestinal tract, and respiratory tract. However, the rat model was calibrated against data on the above tissues, only for single dose intratracheal or intravenous exposures. Evaluations of predictions for repeated-dose exposures have been limited to blood concentration kinetics in an acute repeated dose inhalation exposure; and for terminal bone, kidney, and liver chromium levels in a 1-year drinking water study. The human model has been calibrated against data on plasma and red blood cell chromium concentrations and urinary chromium excretion following single oral doses administered to humans. Evaluation of predictions of repeated-dose outcomes have been limited to plasma and urine chromium kinetics, based on a study of a single subject exposure to chromium(VI) in drinking water for 17 days.

Species extrapolation. Evaluation of the robustness of extrapolation of the rat or human models to other species has not been reported.

Interroute extrapolation. The rat and human models include parameters for simulating inhalation and ingestion of chromium. The rat model was calibrated against data from single-dose intratracheal or intravenous exposures, and was evaluated against repeated-dose studies of inhaled and ingested chromium. The human model was calibrated and evaluated with data from ingestion studies; evaluation of the robustness of the model for predicting chromium kinetics following exposures to other routes has not been reported.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The absorption of inhaled chromium compounds depends on a number of factors, including physical and chemical properties of the particles (oxidation state, size, solubility) and the activity of alveolar macrophages. Chromium has been identified in the tissues of occupationally-exposed humans, suggesting that chromium can be absorbed from the lungs (Cavalleri and Minoia 1985; Gylseth et al. 1977; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Tossavainen et al. 1980). Animal studies have also demonstrated increased amounts of chromium in the blood following inhalation or intratracheal instillation exposures (Baetjer et al. 1959b; Bragt and van

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Dura 1983; Langård et al. 1978; Visek et al. 1953; Wiegand et al. 1984, 1987). Chromium(VI) is more rapidly absorbed into the bloodstream than is chromium(III) (Gao et al. 1993; Suzuki et al. 1984). Chromium that is not absorbed in the lungs may be cleared via mucociliary clearance and enter the gastrointestinal tract.

Chromium is poorly absorbed from the gastrointestinal tract; the primary site of chromium absorption appears to be the jejunum (Donaldson and Barreras 1966). The bioavailability of chromium compounds seems to be most dependent on the oxidation state of the chromium atom. However, other factors, including formulation of the chromium, can influence the extent of absorption. Inorganic chromium(III) is very poorly absorbed, with only 0.5–2.8% of dietary chromium absorbed via the gastrointestinal tract of humans (Anderson 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Gargas et al. 1994; Kerger et al. 1996a; Kuykendall et al. 1996). Human studies demonstrate that chromium(VI) is effectively reduced to chromium(III) by gastric juices (De Flora et al. 1987a) and in general, chromium(VI) is better absorbed than chromium(III) following oral exposure in humans (Donaldson and Barreras 1966; Finley et al. 1996b; Kerger et al. 1996a; Kuykendall et al. 1996). Absorption efficiencies ranging from 1.7 to 6.9% have been estimated in humans (Finley et al. 1996a; Kerger et al. 1996a, 1997; Kuykendall et al. 1996). Ingestion of chromium with a meal appears to increase the absorption efficiency (Chen et al. 1973).

Both chromium(III) and chromium(VI) can penetrate human skin to some extent, especially if the skin is damaged. Following dermal exposure, chromium has been detected in the blood, feces, and urine of exposed humans (Brieger 1920), though in this study, the skin was damaged, which likely facilitated absorption. An average rate of systemic uptake of chromium(VI) in humans submersed in chlorinated water containing potassium dichromate(VI) for 3 hours was 1.5×10^{-4} $\mu\text{g}/\text{cm}^2\text{-hour}$ (Corbett et al. 1997). Chromium(VI) appears to penetrate the skin faster than chromium(III) (Mali et al. 1963; Spruit and van Neer 1966; Wahlberg 1970), though many other factors may be involved, including solvent (Liden and Lundberg 1979) and concentration (Baranowska-Dutkiewicz 1981).

Absorbed chromium is carried throughout the body in the blood, eventually being distributed to all tissues. Greatest concentrations of chromium are found in the blood, liver, lung, spleen, kidney, and heart (Kaufman et al. 1970; Schroeder et al. 1962; Teraoka 1981). Because insoluble chromium is not completely cleared or absorbed following inhalation exposure, greater levels of chromium are often found in lung tissues following inhalation of chromium compounds than following other methods of exposure. Tissue levels appeared to be higher after exposure to chromium(VI) than to chromium(III). This may be due to the greater ability of chromium(VI) to cross cell membranes and may also be a function of

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administration of doses high enough to overwhelm the chromium(VI) reduction mechanisms. De Flora et al. (1997) have demonstrated that liver, erythrocytes, whole blood, lung epithelial fluid, alveolar macrophages, and peripheral parenchyma cells all have the ability to reduce chromium(VI) to chromium(III). Chromium has been detected in breast milk (Casey and Hambidge 1984; Shmitova 1980), but the relationship between chromium exposure, dietary or otherwise, and breast milk chromium levels is inconclusive (Anderson et al. 1993; Engelhardt et al. 1990; Mohamedshah et al. 1998).

Systemic chromium(III) does not appear to be stored for extended periods of time within the tissues of the body. However, the prolonged half-life of chromium(VI) compared to chromium(III) in humans (Kerger et al. 1997) and animals indicate that a portion of the absorbed chromium(VI) dose that is not converted to chromium(III) is being sequestered inside cells. Single- and multiple-exposure studies in humans have shown a one-compartment clearance half-time in humans on the order of 36 hours (Kerger et al. 1997; Paustenbach et al. 1996) following oral exposure. This half-time is sufficiently long to allow for accumulation of chromium following regular repeated exposure. Following inhalation exposure, insoluble chromium that is not cleared from the lungs may remain for a considerable time. In the blood, chromium(VI) is taken up by erythrocytes and reduced to chromium(III) which forms complexes with hemoglobin and other intracellular macromolecules; these complexes are retained within the erythrocyte for the life-span of the cell (Paustenbach et al. 2003).

Inhaled chromium can be eliminated from the lungs by absorption into the bloodstream, by mucociliary clearance, and by lymphatic system clearance (Bragt and van Dura 1983; Perrault et al. 1995; Visek et al. 1953; Wiegand et al. 1984, 1987). The primary routes of elimination of absorbed chromium is urine and feces. It can also be eliminated in hair and fingernails (Randall and Gibson 1989; Stearns et al. 1995a; Takagi et al. 1986). Chromium, once reduced to chromium(III) in the liver, is then conjugated with glutathione and enters bile where it is excreted in the feces (Norseth et al. 1982). Because chromium is poorly absorbed following oral exposure, a large percentage of the amount ingested is excreted in the feces. The half-time of urinary excretion of chromium is short, 4–10 hours for inhalation exposure (Kiilunen et al. 1983), 10 hours for oral exposure to chromium(III) (Kerger et al. 1996a), and 40 hours for oral exposure to chromium(VI) (Kerger et al. 1996a, 1997). Following dermal exposure, chromium that is not absorbed into the bloodstream will remain on the skin until it is eliminated, usually by washing or other physical processes. Absorbed chromium is primarily eliminated in the urine.

3.5.2 Mechanisms of Toxicity

The toxic potency of chromium is dependent on the oxidation state of the chromium atom, with chromium(VI) more potent than chromium(III). The mechanisms of chromium toxicity and carcinogenicity are very complex. They are mediated partly through reactive intermediates during intracellular reduction of chromium(VI) to chromium(III) and oxidative reactions, and partly mediated by chromium(III) which is the final product of intracellular chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Salnikow and Zhitkovich 2008; Shrivastava et al. 2002; Yao et al. 2008; Zhitkovich 2005). Chromium(III) may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, and alterations in cellular signaling pathways, which may contribute to toxicity and carcinogenicity of chromium compounds.

The greater toxic potency of chromium(VI) relative to chromium(III) most likely is related to two factors: (1) the higher redox potential of chromium(VI) (Levina and Lay 2005; Reddy and Chinthamreddy 1999); and (2) the greater ability of chromium(VI) to enter cells (Costa 2003). Differences in molecular structure contribute the greater cellular uptake of chromium(VI) compared to chromium(III) (Costa 2003; Costa and Klein 2006a). At physiological pH, chromium(VI) exists as the tetrahedral chromate anion, resembling the forms of other natural anions (e.g., sulfate and phosphate) which are permeable across nonselective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to chromium(III) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

The higher redox potential of chromium(VI) contributes to the higher toxic potency of chromium(VI) relative to chromium(III) (Levina and Lay 2005), because once it is taken into cells, chromium(VI) is rapidly reduced to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Hojo and Satomi 1991; Kim and Yurkow 1996; Lin et al. 1992; Liu et al. 1997b; Mao et al. 1995; Wiegand et al. 1984; Zhitkovich et al. 1996). Chromium(VI), chromium(V), and chromium(IV) have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species (Aiyar et al. 1991; Chen et al. 1997; Liu et al. 1997b;

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Luo et al. 1996; Mao et al. 1995; Molyneux and Davies 1995; Tsou et al. 1996). It is believed that the formation of these radicals, which leads to oxidative stress, may be responsible for many of the deleterious effects of chromium on cells, including lipid peroxidation (Bagchi et al. 2002a; Hojo et al. 1999, 2000) and alterations in cellular communication, signaling pathways and cytoskeleton (Chen et al. 1997; Gao et al. 2002; Gunaratnam and Grant 2002, 2004; Kim and Yurkow 1996; Mikalsen 1990; O'Hara et al. 2007; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Yao et al. 2008; Ye et al. 1995). The chromium(VI)-induced oxidative stress resulting from the generation of reactive oxygen species has been shown in *in vitro* studies to result in the induction and inhibition of the transcription factors, NF- κ B and AP-1, activation of p53, activation of hypoxia-inducible factor 1 (HIF-1), cell-cycle arrest, and p53-dependent apoptosis (Yao et al. 2008). Cellular damage from exposure to various chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (Hojo et al. 2000; Luo et al. 1996; Tsou et al. 1996; Ueno et al. 1995a).

The products of metabolic reduction of chromium(VI) (free radicals and chromium(IV) and (V)) and the newly generated chromium(III) are thought to be in part responsible for the carcinogenic effects seen in human and animal studies. The interaction of free radicals, chromium(V), chromium(IV), and chromium(III) with DNA can result in structural DNA damage, functional damage, and other cellular effects (Levina and Lay 2005; Singh et al. 1998a). The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al. 2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Functional damage includes DNA polymerase arrest (Bridgewater et al. 1994a, 1994b, 1998), RNA polymerase arrest, mutagenesis, and altered gene expression. However, DNA double strand breaks may not be due to free radical formation, but due to the formation of chromium-DNA ternary adducts, which lead to repair errors and collapsed replication forks (Ha et al. 2004). Double strand breaks can also lead to alterations in cellular communication and effects on signaling pathways and cytoskeleton. In addition, results of recent studies in human lung cells suggest that chromosome instability is an important mechanism in the development of lung cancers; specifically, chromium-induced chromosome

instability appears to be mediated through centrosome and spindle assembly checkpoint bypass (Holmes et al. 2006; Wise et al. 2006a).

Location of particle deposition in the lung and extracellular dissolution of chromium(VI) compounds (e.g., solubility) are also important considerations regarding the mechanism of chromium(VI)-induced carcinogenesis. In chromate workers, analysis of bronchial tissues shows higher chromium concentrations in areas of bronchial bifurcation compared to other areas in the bronchi (Ishikawa et al. 1994a). Also, autopsy results show that some precancerous bronchial lesions originated at bronchial bifurcations (Ishikawa et al. 1994b). Solubility of chromium(VI) compounds may also play a role in carcinogenic potency, with extracellular dissolution of the chromium compound critical to activity (Wise et al. 2004). This hypothesis is supported by *in vitro* data suggesting that extracellular chromium ions are the proximate clastogen in Chinese hamster ovary cells (Wise et al. 2004).

Chromium(III) can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor- κ B, or may inhibit regulatory genes such as GRP78 (Chen et al. 1997; Kim and Yurkow 1996; Manning et al. 1992; Mikalsen 1990; O'Hara et al. 2003; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest (Xu et al. 1996) and apoptosis (Carlisle et al. 2000; Singh et al. 1999). Numerous studies show that chromium can induce apoptosis (Asatiani et al. 2004; Bagchi et al. 2001; Carlisle et al. 2000; Flores and Perez 1999; Gambelunghe et al. 2006; Gunaratnam and Grant 2002, 2004; He et al. 2007; Manyoats et al. 2002; Petit et al. 2004; Russo et al. 2005; Vasant et al. 2003); although the mechanism by which chromium induces apoptosis is not fully understood, it is believed to involve oxidative stress and activation of the p-53 protein (Pulido and Parrish 2003; Singh et al. 1998a).

3.5.3 Animal-to-Human Extrapolations

Species-related differences in chromium pharmacokinetics have been demonstrated, both between rodent species and between rodents and humans. However, studies directly examining species differences have been limited. Human microsomal chromium(VI) reduction is different from the P450-mediated microsomal reduction in rodents; specifically, the human system is much less oxygen-sensitive, has a much greater affinity for chromate, and is apparently mediated by flavoproteins (Myers and Myers 1998; Pratt and Myers 1993). Tissue distributions of chromium were found to be different between rats and

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mice after administration of bolus amounts of chromium(VI). Rat erythrocytes had a greater capacity to sequester chromium(VI) and reduce it to chromium(III) than mouse erythrocytes (Coogan et al. 1991b; Kargacin et al. 1993), thus demonstrating that both physiologic and metabolic differences can exist among species.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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Based on results of *in vivo* and *in vitro* studies, chromium(VI) may alter function of the hypothalamic-pituitary axis function. Serum prolactin levels were decreased by 59% in male Wistar rats exposed to 74 mg chromium(VI)/kg/day as potassium dichromate in drinking water for 30 days. Incubation of cultured rats anterior pituitary cells with 0.1–10 μ M chromium(VI) as potassium dichromate decreased prolactin secretion and cell viability (Quinteros et al. 2007). No additional assessments of hypothalamic-pituitary axis function were conducted in this study. Exposure of female rats to 11.4 mg chromium(VI)/kg/day as potassium dichromate during lactation days 1–21 resulted in delayed ovarian follicle development and pubertal onset and impaired ovarian steroidogenesis in female offspring (Banu et al. 2008). In *in vitro* experiments with immortalized granulosa cells, chromium decreased mRNA expression of a number of steroidogenic enzymes and steroidogenesis regulatory factors (Banu et al. 2008). Serum testosterone levels were decreased by 20.8% in male New Zealand rabbits administered 3.6 mg chromium(VI)/kg/day as potassium dichromate for 10 weeks by gavage (Yousef et al. 2006); however, since function of the hypothalamic-pituitary-gonadal axis was not assessed, it is unclear if this effect reflects endocrine disruption.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics

and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990b; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Chromium(III) is an essential nutrient required for maintaining normal glucose metabolism. The IOM of the NAS determined an adequate intake of 0.2 µg chromium/day for infants aged 0–6 months; 5.5 µg chromium/day for infants aged 7–12 months; 11 µg chromium/day for children aged 1–3 years; 15 µg chromium/day for children aged 4–8 years; 25 µg chromium/day for boys aged 9–13 years; 21 µg chromium/day for girls aged 9–13 years; 35 µg chromium/day for boys aged 14–18 years; and 24 µg chromium/day for girls aged 14–18 years (IOM 2001).

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There is a limited amount of information available on the toxicity of chromium in children. Most of the available data come from several case reports of children ingesting lethal concentrations of chromium(VI). A variety of systemic effects were observed in a 22-month-old who accidentally ingested an unknown amount of sodium dichromate (Ellis et al. 1982), a 1-year-old who ingested an unknown amount of ammonium dichromate (Reichelderfer 1968), a 17-year-old who intentionally ingested 29 mg chromium(VI)/kg as potassium dichromate (Clochesy 1984; Iserson et al. 1983), and a 14-year-old who ingested 7.5 mg chromium(VI)/kg as potassium dichromate (Kaufman et al. 1970). The effects included pleural effusion, bronchopneumonia, hypoxic changes in the myocardium, decreased blood pressure and cardiac output, abdominal pain and vomiting, gastrointestinal burns and hemorrhage, and liver and kidney necrosis. An enlarged brain and cerebral edema were also observed in the 14-year-old (Kaufman et al. 1970). These effects are similar to effects observed in adults who have ingested lethal doses and are part of the sequelae leading to death.

A number of additional health effects have been observed in adults exposed to chromium (primarily chromium(VI)) at work. The primary targets appear to be the respiratory tract, gastrointestinal tract, hematological system, liver, and kidneys; an increased cancer risk has also been observed. Dermal contact in chromium sensitized individuals can lead to an allergic type dermatitis. In the absence of data to the contrary, it is likely that these organs/systems will also be sensitive targets in children. There is insufficient information to determine whether the susceptibility of children would differ from that of adults.

Although there are no human studies that examined developmental end points, animal studies have consistently shown that chromium, particularly chromium(VI), is a developmental toxicant. A number of developmental effects have been reported in oral studies involving maternal exposure to ≥ 2.9 mg chromium(VI)/kg/day as potassium dichromate (Al-Hamood et al. 1998; Junaid et al. 1996b; Samuel et al. 2011; Trivedi et al. 1989). The observed effects included increases in postimplantation losses, gross abnormalities (e.g., subdermal hemorrhage, decreased ossification, kinky tail), and impaired development of the reproductive system (e.g., impaired fertility in female offspring, delayed vaginal opening, altered estrous cycling). Similar developmental effects (e.g., post implantation losses, subdermal hemorrhage, decreased ossification) have also been observed in the offspring of rats and mice exposed to ≥ 37 mg chromium(VI)/kg/day for 20 or 90 days prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998). Conflicting results have been found for chromium(III). No developmental effects were reported in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout gestation (Ivankovic and Preussmann 1975). However, impaired development of the

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reproductive system (decreased reproductive tissue weight and impaired fertility) were observed in the offspring of mice exposed to 74 mg chromium(III)/kg/day as chromium chloride (Al-Hamood et al. 1998). Exposure to 25 mg chromium(III)/kg/day as chromium picolinate during gestation and lactation did not affect the neurological development of the offspring (Bailey et al. 2008a). Developmental effects have also been observed following intraperitoneal administration of chromium(III) chloride (Iijima et al. 1983; Matsumoto et al. 1976).

Chromium may be transferred to fetuses through the placenta and to infants via breast milk. Elevated levels of chromium have been reported in umbilical cord blood, placentae, and breast milk of women working in a dichromate(VI) manufacturing facility (Shmitova 1980). As noted elsewhere in the profile, the reliability of this study is suspect because the levels of chromium in the blood and urine of the control women were much higher than background levels. Measurement of the chromium content in 255 samples from 45 lactating American women revealed that most samples contained $<0.4 \mu\text{g/L}$, and the mean value was $0.3 \mu\text{g/L}$ (Casey and Hambidge 1984). While these probably represent background levels in women whose main exposure to chromium is via the diet, the findings indicate that chromium may be transferred to infants via breast milk. These findings in humans are supported by animal data. Studies in rats and mice have shown that chromium(VI) and chromium(III) crosses the placenta and enters into fetal tissue. Elevated levels of chromium have been observed in the placenta and fetal tissue of rats and mice exposed to potassium dichromate(VI) in drinking water during pregnancy (Saxena et al. 1990a). The levels of chromium in the placenta were 3- and 3.2-fold higher in the exposed rats and mice, respectively, than in controls and fetal tissue chromium levels were 3.1- and 9.6-fold higher, respectively; the difference over control was only statistically significant in the mice. Another study (Danielsson et al. 1982) also found elevated fetal tissue levels of chromium. The chromium levels in the fetal tissues were 12–19% of maternal blood levels following maternal intravenous injections of sodium dichromate(VI) on gestational days 12–15 or 16–18 and 0.4–0.8% following maternal intravenous injections of chromium(III) trichloride on gestational days 12–15 or 16–18. A study of transplacental transfer of chromium(III) in different forms indicated that placental transport varies with the chemical form (Mertz et al. 1969). Higher levels of chromium were found in the neonates of rats fed chromium in a commercial diet as compared to neonates of rats fed a chromium-deficient diet and given drinking water containing chromium acetate monohydrate. Similarly chromium levels were significantly elevated in the offspring of rats administered chromium in the form of chromodulin from Brewer's yeast by gavage than in the offspring of rats administered chromium trichloride intravenously or by gavage.

There is very little information available in which to assess whether the pharmacokinetic properties of chromium would be different in children. Sullivan et al. (1984) found that gastrointestinal absorption of radiolabeled chromium chloride, administered by gavage, was 10 times higher in 2-day-old rats as compared to levels absorbed in adult rats. A similar pattern of distribution in the body was found in the immature and mature rats.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to chromium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chromium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Chromium

As an essential nutrient, chromium is normally present in blood and urine. Chromium in body fluids (e.g., blood and urine) is the exposure biomarker of choice. Mean dietary chromium intake in the general U.S. population was estimated as 0.505 $\mu\text{g/kg/day}$ (equivalent to 35.35 $\mu\text{g/day}$, assuming a body weight of 70 kg), with a range of 0.293–0.867 $\mu\text{g/kg/day}$ (Moschandreas et al. 2002); however, only a small amount of dietary chromium is absorbed ($\leq 3\%$). The IOM of the NAS (IOM 2001) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 $\mu\text{g chromium(III)/day}$ for adolescents and adults. Daily dietary intake levels have been shown to correlate with total excretion of chromium in the urine and feces (Bunker et al. 1984). The IOM (2001) reported average plasma chromium concentrations of 2–3 nmol/L (equivalent to 0.10–0.16 $\mu\text{g/L}$) and an average urinary chromium excretion of 0.22 $\mu\text{g/L}$ or 0.2 $\mu\text{g/day}$; endogenous chromium concentrations also have been reported as 0.01–0.17 $\mu\text{g/L}$ (median 0.06 $\mu\text{g/L}$) in serum (Sunderman et al. 1989), 0.24–1.8 $\mu\text{g/L}$ (median 0.4 $\mu\text{g/L}$) in urine (Iyengar and Woittiez 1988), and 0.234 mg/kg in hair (Takagi et al. 1986). However, normal chromium levels in human fluid and tissues should be interpreted with caution. The low sensitivity of the most commonly used detection methods and the ubiquitous presence of chromium in laboratories make detection of low levels of chromium in blood and urine difficult.

Exposure to chromium may result in increased chromium concentrations in blood (whole blood, serum, and erythrocytes), urine, expired air, hair, and nails; of these, elevations of chromium in blood and urine are considered the most reliable indicators of exposure (Barceloux 1999; Caglieri et al. 2006). Urinary elimination half-times for absorbed chromium(III) range from 10–40 hours (Kerger et al. 1996a). Assuming an elimination half-time of 40 hours, steady state, plasma concentration, and urinary excretion rate of chromium would reach 95% of steady state levels in approximately 7 days (Paustenbach et al. 1996). Once steady state is achieved, the daily amount of chromium excreted in urine will reflect the daily amount absorbed. With cessation of exposure levels of chromium in plasma and urine will reach 5% of steady state within 7 days. The relatively rapid elimination kinetics of absorbed chromium(III) has

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implications for the use of plasma and urine as biomarkers of exposure to chromium. Plasma and urinary chromium concentrations will largely reflect relatively recent exposure (i.e., exposures that occurred several weeks prior to the sample may not be detected from plasma or urinary chromium measurements). During relatively constant or repetitive exposures that achieve a steady state in plasma, daily urinary chromium excretion measured on a single day can be expected to be highly correlated with chromium intake. This correlation will weaken with greater intermittency in the exposure, with greater dependence on the time of sampling with respect to the most recent exposure. The above general principles apply to exposures to absorbed chromium(III) compounds; however, absorbed chromium(VI) has a longer retention time in blood. Chromium(VI) that enters blood is taken up by red blood cells, reduced to chromium(III), and, in the process, form adducts with red blood cell hemoglobin and other proteins. These complexes are sufficiently stable to remain in the red blood cells for a substantial fraction of the lifespan of the red blood cell. Therefore, following absorption of chromium(VI) into blood, the elimination half-time of chromium in blood will be substantially longer than that in plasma. The elimination half-time of injected chromium(VI) (e.g., sodium chromate-51, used in the clinical assessment of red blood cell volume) is approximately 25–35 days (Dever et al. 1989). Based on a half-time of 30 days in red blood cells, with cessation of exposure to and absorption of chromium(IV), levels of chromium in red blood cells will reach 5% of a previous steady state level within 130 days.

Although chromium also accumulates in white blood cells, erythrocyte chromium has been shown to be a more sensitive measure of chromium exposure (Coogan et al. 1991b; Lukanova et al. 1996). An increase in plasma levels of chromium may reflect both recent exposure and exposure that occurred during the past few months (e.g., chromium that is sequestered within erythrocytes for the lifespan of the cell), whereas elevated urine chromium primarily reflects exposure over the past 1–2 days (Barceloux 1999). Distinct measurements of chromium in plasma and whole blood (reflecting intracellular distribution to erythrocytes) may also be useful in distinguishing exposures to chromium(VI) compounds versus chromium(III) compounds; increased plasma levels of chromium may indicate exposure to both chromium(VI) and chromium(III), whereas increased chromium in erythrocytes indicates exposure to chromium(VI), since chromium(III) is not taken up by erythrocytes. For example, evaluation of postshift whole blood, serum, erythrocytes, and urine in groups of dichromate production workers exposed mainly to chromium(VI) or chromium(III) showed relationships between exposure type (e.g., chromium(VI) or chromium(III)) and chromium in blood and urine (Minoia and Cavalleri 1988). In 22 workers exposed primarily to chromium(VI) (0.008–0.212 mg chromium(VI)/m³, 0.010–0.10 mg chromium(III)/m³), the mean postwork-shift urinary chromium level was 31.5 µg total chromium/L; chromium(VI) was not detected in the urine samples (detection limit=0.05 µg chromium(VI)/L) due to *in vivo* reduction of

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chromium(VI) to chromium(III). Concentrations of total chromium in serum, erythrocytes, and whole blood were 2.2, 8.9 and 6.9 µg/L, respectively; compared with control levels of 1.1, 1.0, and 1.4 µg/L, respectively. In 15 workers exposed primarily to chromium(III) (0.046–1.689 mg chromium(III)/m³, 0.002–0.023 mg chromium(VI)/m³), the mean postwork-shift urinary chromium level was 24.7 µg total chromium/L and concentrations of total chromium in serum, erythrocytes, and whole blood were 3.1 µg/L, 1.4, and 1.8, respectively. The level of chromium in serum of the workers exposed mainly to chromium(III) was significantly ($p<0.001$) higher than that measured in workers exposed mainly to chromium(VI) or in controls. The level of chromium in erythrocytes of the workers exposed mainly to chromium(III) was significantly ($p<0.001$) less than that in workers exposed mainly to chromium(VI). The finding of higher levels of chromium in serum and lower levels of chromium in erythrocytes of workers exposed mainly to chromium(III) than in workers exposed mainly to chromium(VI) reflects the relative inability of chromium(III) to enter erythrocytes.

Although exposure to chromium may produce increases in chromium levels in both blood and urine chromium levels, the relationship between blood and urinary chromium levels may vary. Entry of chromium(VI) into the red blood cells probably reflects a competition between plasma reduction to chromium(III) and red blood cells uptake of chromium(VI) and not the result or consequence of the exhaustion of plasma reducing ability. When hexavalent chromium is incubated with washed isolated erythrocytes, almost all of the entire dose is taken up by the cells. Chromium(VI) is then reduced inside the cells to trivalent chromium, essentially trapping it inside the erythrocyte. In contrast, little chromium(III) appears to be taken up by erythrocytes *in vitro* incubations (Aaseth et al. 1982; Bentley 1977; Donaldson and Barreras 1966; Gray and Sterling, 1950). When chromium(VI) is incubated with whole blood or erythrocytes plus plasma, only a fraction (depending on conditions) of the chromium(VI) is taken up by the erythrocytes (Coogan et al. 1991b; Corbett et al. 1998; Lewalter et al. 1985; Wiegand et al. 1985), most likely due to the reduction of a portion of chromium(VI) to chromium(III) outside of the erythrocyte (Capellmann and Bolt 1992; Korallus et al. 1984; Richelmi et al. 1984). Thus, chromium(III) is then largely excluded from the erythrocyte. However, Korallus (1986a, 1986b) has proposed that the relationship between blood and urinary chromium levels may vary, possibly due to variability in plasma reduction capacity. *In vitro* experiments indicate that when chromium(VI) plasma levels exceed the plasma reduction capacity (PRC), chromium(VI) enters erythrocytes, is reduced, and binds to hemoglobin. The bond persists for the lifetime of the erythrocytes (120 days); therefore, a single determination of chromium in erythrocytes allows a longitudinal evaluation of exposure for an extended period in the past. Low chromium concentrations in erythrocytes indicate that the amount of chromium(VI) uptake did not exceed the PRC. Limited evidence suggests that the capacity of human

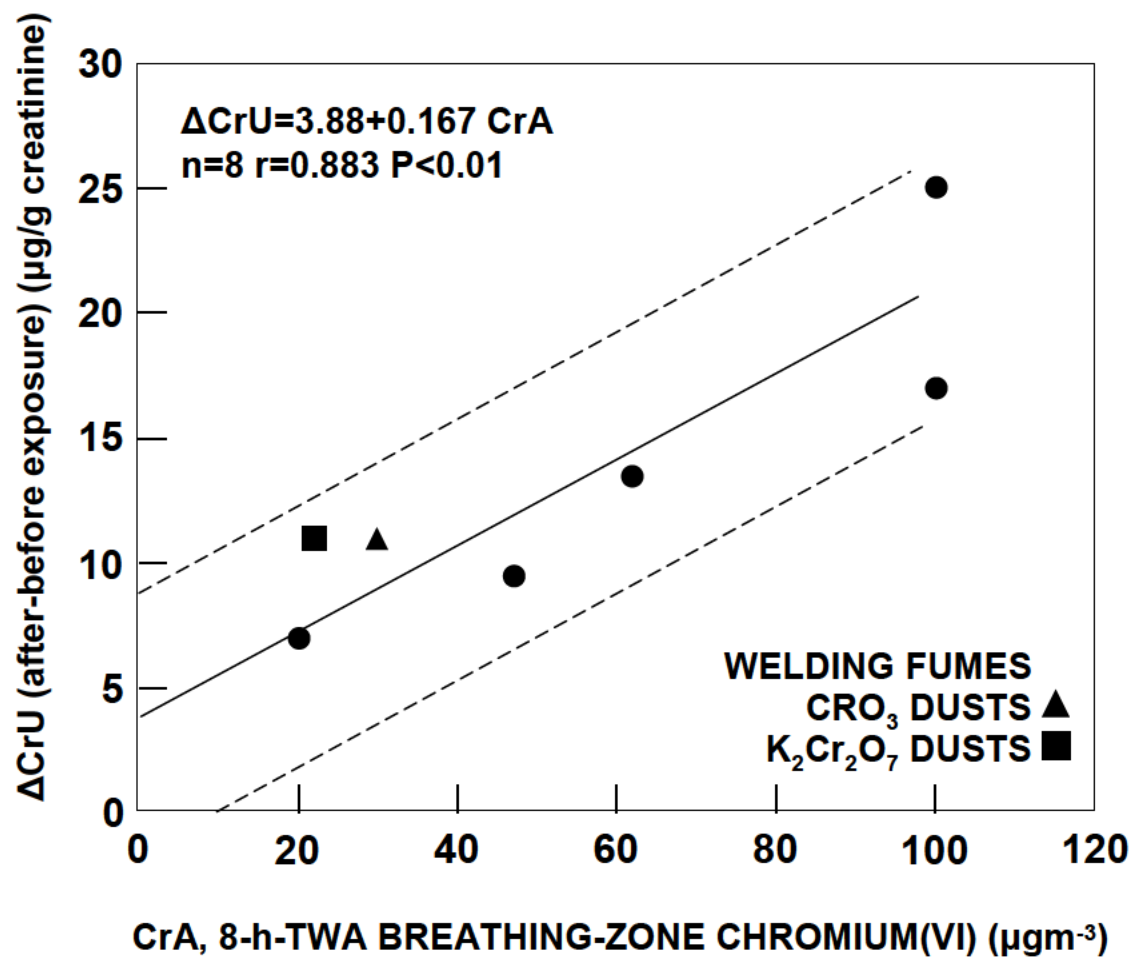
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plasma to reduce chromium(VI) compounds to chromium(III) compounds varies, with slow and fast reducers recognized (Korallus 1986a, 1986b). It is not clear what is responsible for individual differences in the PRC, although difference in magnitude of PRC appears to correlate with the levels of ascorbic acid in plasma.

The relationship between serum and urine chromium levels to occupational exposure levels has been investigated in numerous studies, with results showing correlations between exposure levels and chromium levels in blood and urine (Gylseth et al. 1977; Iarmarcovai et al. 2005; Kilburn et al. 1990; Lewalter et al. 1985; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Medeiros et al. 2003a; Minoia and Cavalleri 1988; Muttamara and Leong 2004; Mutti et al. 1985b; Randall and Gibson 1987, 1989; Saner et al. 1984; Sathwara et al. 2007; Simpson and Gibson 1992; Sjogren et al. 1983; Stridsklev et al. 2004; Takagi et al. 1986; Tola et al. 1977; Wiegand et al. 1988). In workers exposed to chromium(VI) as chromium trioxide in the chrome plating industry, a significant correlation ($r=0.71$) was observed between exposure levels and postshift urinary chromium; for a TWA exposure of $0.002 \text{ mg chromium(VI)/m}^3$, the mean urinary chromium level was $5.2 \text{ }\mu\text{g/L}$ (excluding workers with obvious skin contamination) (Lindberg and Vesterberg 1983a). Significant correlations were observed between chromium concentrations in air (measured by personal sampling devices; 8-hour TWA) and levels of chromium in blood ($r=0.99$) and urine ($r=0.89$) in workers at a chromium alloy facility (Muttamara and Leong 2004). In areas of low exposure, the air concentration of chromium (type not specified) was $5.75 \text{ }\mu\text{g/m}^3$; in workers in this area, mean chromium concentrations in blood and urine (duration of sample collection was not reported) were 0.925 and $0.095 \text{ }\mu\text{g/dL}$, respectively. In areas of high exposure, the air concentration of chromium was $7.25 \text{ }\mu\text{g/m}^3$, in workers in this area, mean chromium concentrations in blood and urine were 3.64 and $0.34 \text{ }\mu\text{g/dL}$, respectively. An increase in urinary chromium of $12.2 \text{ }\mu\text{g/g creatinine}$ above preexposure values or a total concentration of $29.8 \text{ }\mu\text{g/g creatinine}$ (end-of-shift values) corresponded to an air concentration of $50 \text{ }\mu\text{g chromium(VI)/m}^3$ from welding fumes (Mutti et al. 1985b). Examination of end-of-shift chromium levels indicated a correlation between urinary chromium levels and exposure to soluble chromium(VI) compounds, but not to insoluble chromates or chromium(III) compounds (Minoia and Cavalleri 1988; Mutti et al. 1985b). The relationship between workroom air concentrations of water soluble chromium(VI) compounds and daily increases in urinary chromium (preexposure values subtracted from end-of-shift values) are shown in [Figure 3-7](#). Serum and urine concentrations of chromium were significantly elevated in a group of 73 tannery workers, with exposure primarily to chromium(III) compounds, compared to a group of 52 control subjects, at the end of the workweek on Friday and before exposure began on Monday (Randall and Gibson 1987). Serum and urine chromium levels correlated with work area of the tannery,

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Figure 3-7. Relationship Between Water Soluble Chromium(VI) CrA and Daily Increase in Urinary Chromium Levels (CrU) (Pre-exposure Values were Subtracted from End-of-Shift Values)



Source: Mutti et al. 1985b

with the highest concentrations in workers handling wet hides in the chrome tanning and wringing departments. The time-weighted average level of total chromium in tannery air was $1.7 \mu\text{g}/\text{m}^3$ and did not vary significantly among the various tanneries involved in the study or among the various work areas of each tannery, with chromium(VI) levels in tannery air below the detection limit of ($0.1 \mu\text{g}/\text{m}^3$).

Urinary and blood chromium have also been used as a biomarker for environmental exposure (Bukowski et al. 1991; Chang et al. 2006; Fagliano et al. 1997). However, interpretation of results may be limited by several factors, including that exposure must be sufficient such that urinary and blood concentrations are higher than the range of background concentrations and analytical limit of detection, high inter- and intrapersonal variability, and that different chemical forms have different bioavailabilities (Paustenbach et al. 1997; Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997). Furthermore, the short half-life of chromium (e.g., at least 90% of absorbed chromium is eliminated within 24 hours) make it difficult to assess exposure incidents. Low-level, intermittent exposure, such as would occur with environmental exposures to soil, dust, and residential drinking water, may not be detected with urinary monitoring; however, it is more likely that urinary monitoring would detect higher-level continuous exposure or daily inhalation exposure to chromium(VI). Paustenbach et al. (1997) note that chromium intakes would have to exceed $2 \mu\text{g}/\text{day}$ in order to distinguish the exposure from background. Large interpersonal variability (as high as a factor of 10) and intrapersonal variability (as high as a factor of 3) can result in highly variable erroneous conclusions regarding significant differences among populations.

3.8.2 Biomarkers Used to Characterize Effects Caused by Chromium

Chromium has been shown to produce effects to several systems, including the respiratory, gastrointestinal, hematological, and immunological systems (see Section 3.2); however, many of these effects are not specific for chromium. Although effects to these physiological systems can be assessed with blood and respiratory function tests and by physical examination, these assessments would not serve as biomarkers specific for effects of chromium as impairment of these systems can result from a variety of other causes, including chemical toxicity, nutritional insufficiencies, and disease.

Occupational exposure to chromium and its compounds has caused respiratory effects, such as pneumonitis, impaired pulmonary function, nasal septum perforations, irritation of the mucosa, inflammation, and cancer. In addition, chromium can be irritating and corrosive to the skin. Chromium exposure may cause asthma attacks and dermatitis in sensitive individuals. Workers with urinary levels of chromium $>15 \mu\text{g}/\text{g}$ creatinine had increased retinol binding protein and tubular antigens in the urine.

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The workroom levels ranged from 0.05 to 1.0 mg chromium(VI)/m³ as chromium trioxide (Franchini and Mutti 1988). The urine of chromium(VI) exposed workers in a chromate production plant contained higher levels of a brush border protein and of retinol-binding protein in the urine than did nonexposed controls (Mutti et al. 1985a). In a study of currently exposed chrome platers, ex-chrome platers, and referent groups of nonexposed workers, the urinary levels of β_2 -microglobulin were significantly higher ($p=0.045$), and elevated levels occurred more often in the presently exposed groups compared with its age-matched control group. The levels of β_2 -microglobulin in the urine of the ex-chrome platers, however, were not different than those of its age-matched control group (Lindberg and Vesterberg 1983b). Another study of hard chrome electroplaters found a higher prevalence of workers with elevated N-acetyl- β -glucosaminidase levels (Liu et al. 1998). Although this study also found higher levels of β_2 -microglobulins in the chrome plater, the prevalence of elevated values was not significantly increased. The presence of low molecular weight proteins, such as retinol binding protein, antigens, or β_2 -microglobulin in the urine is believed to be an early indication of kidney dysfunction. The lack of a significant difference in the ex-chrome platers compared with the control group suggests that the chromium-induced kidney damage may be reversible. Cell culture and cell free studies discussed in Section 3.5.2 demonstrated that chromium forms protein-DNA crosslinks and adducts with DNA, and that these end points may be potentially useful biological markers, indicating the possibility of genotoxic effects or cancer in humans exposed to chromium. However, no increases in protein-DNA crosslinks were observed in white cells from volunteers who were exposed to chromium(VI) in drinking water (Kuykendall et al. 1996).

The possibility of using an immune-function assay as a potential biomarker for humans exposed to chromium has been examined (Snyder et al. 1996). Isolated mononuclear cells from 46 individuals who lived and/or worked in areas in northern New Jersey at sites contaminated by chromium processing were stimulated by pokeweed mitogen. Rates of stimulated cell growth and production of interleukin 6 (IL-6) were measured and compared to a control population of people who lived/worked in uncontaminated areas. There was no significant increase in mitogen stimulation between people from contaminated areas and controls, but there was a significant (36%) decrease in the levels of IL-6 in monocytes in the chromium exposed group. IL-6 is an important cytokine that is involved in the T-cell helper pathway of antibody production. The significance of the lower levels may lead to decreased levels of antibody production.

The effects of chromium(III) chloride, sodium chromate(VI), and potassium chromate(VI) on proliferation of mononuclear leukocytes obtained from chromium sensitive individuals (confirmed with

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positive patch tests) was compared to nonsensitive controls (confirmed by negative patch tests) (Räsänen et al. 1991). Isolated cells were exposed to 25–50 µg/mL culture medium of chromium(III) chloride and to 0.025 to 0.1 µg/mL culture medium chromium(VI) salts, which gave optimum responses and cell growth ratios of treated/nontreated cells from eight sensitive individuals ranging from 1.56 to 13.22, average=5.8 (chromium(III)), from 2.24 to 11.43, average 5.4 sodium chromate, and from 1.82 to 9.48, average 5.4 potassium dichromate. The nonsensitive individuals' ratios were consistently lower with ranges from 0.90 to 2.28 and average ratios of 1.14, 1.30, and 1.56, respectively. The authors felt that this *in vitro* methodology could be used diagnostically to assess chromium-sensitive individuals.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990c) and for information on biomarkers for neurological effects see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Potassium dichromate (10 mg/kg) administered by subcutaneous injection potentiated the effects of the nephrotoxins, mercuric chloride, citrinin, and hexachloro-1,3-butadiene, in rats. Effects on renal function included changes in urine volume, osmolality, electrolyte and glucose excretion, and a reduction in renal cortical slice organic ion transport. Chromium(VI) compounds potentiated the effect of mercuric chloride on organic acid uptake but not organic base uptake by renal cortical slices (Baggett 1986; Haberman et al. 1987). A similar experiment with another nephrotoxin, maleic acid, demonstrated the potentiating effect of potassium dichromate (10 mg/kg administered subcutaneously) (Christenson et al. 1989). Christenson et al. (1989) suggested that the combination of potassium dichromate with maleic acid might enhance damage to the brush border of the renal proximal tubules or that damage to the luminal cells by potassium dichromate might allow maleic acid to more easily enter the cells.

Concomitant exposure of female Sprague-Dawley rats to chromium(VI) potassium dichromate and ethanol in drinking water for 22 weeks indicates that ethanol may enhance the hepatic effects of chromium(VI) (Acharya et al. 2001). Serum enzyme activity of ALT in rats treated with 10% ethanol and 25 mg chromium(VI)/L (3.8 mg chromium(VI)/kg/day) was significantly increased compared to treatment of rats with ethanol or chromium(VI) alone. However, the toxicological significance of this finding is uncertain, since serum ALT activities of rats treated with ethanol and chromium(VI) were increased by only 18% compared to treatment of rats with chromium(VI) alone.

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Interactions between selenium in the diet and ammonium dichromate in the drinking water were investigated in a study using rats. During the experiment, one rat died and the other rats had atrophy of the central liver lobe when given selenium alone. Dietary selenium and ammonium chromate in combination caused hepatic necrosis, resulting in the death of four rats (Moxon and DuBois 1939). Although the rats were not fed chromium alone, other studies indicate that the liver is a target for chromium exposure (see Section 3.2). The mechanism for the interaction was not discussed.

Exposure of female hairless mice to ultraviolet light in combination with chromium(VI) as potassium chromate in drinking water at concentrations of 2.5 or 5.0 mg potassium chromate(VI)/L (approximately 0.18 or 0.35 mg chromium(VI)/kg/day) for 182 days, or in the diet at concentrations of 0, 2.5, or 5.0 mg potassium chromate(VI)/kg food (approximately 0.13 or 0.26 mg chromium(VI)/kg/day) for 26 weeks, produced an increased incidence of skin tumors compared to animals exposed to UV light alone or chromium(VI) alone (Davidson et al. 2004; Uddin et al. 2007). Exposure to chromium(VI) alone did not result in neoplasms. The chromium-induced enhancement of UV light-induced skin tumors did not appear to be mediated through oxidative damage, since concomitant treatment with vitamin E or selenomethionine did not decrease the chromium effect.

Concomitant inhalation exposure to ozone and chromium(VI) may alter pulmonary clearance mechanisms in the deep lung (Cohen et al. 2003). Compared to rats treated with insoluble chromium(VI) as calcium chromate (0.34–0.36 mg chromium(VI)/m³) alone for up to 48 weeks, concomitant exposure to ozone (0.59 mg/m³) resulted in decreased particle uptake and altered postphagocytic/endocytic processing of chromium particles by alveolar macrophages. However, since toxicity was not assessed in this study, it is not known if ozone-induced alteration in alveolar macrophage function would result in increased toxicity of chromium(VI).

A number of studies indicate an increase in the mutagenic effects of chromium(VI) compounds in combination with other chemicals. Synergism has been observed between chromium(VI) and 9-aminoacridine, nitrilotriacetic acid, and azide (Bronzetti and Galli 1989; Gava et al. 1989a; LaVelle 1986a, 1986b; Montaldi et al. 1987), but the mechanisms are not clearly understood. Potassium dichromate potentiated mutations produced by sodium azide in *S. typhimurium* or by 9-aminoacridine in *S. typhimurium* and *E. coli*. Although the data were insufficient for speculation on the specific biochemical mechanism, it was suggested that the potentiation involved a specific effect of potassium dichromate on the interaction of 9-aminoacridine or sodium azide with DNA or on subsequent DNA replication and/or repair (LaVelle 1986a, 1986b). Nitrilotriacetic acid, which appears to have no

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genotoxic potential itself, increased the frequencies of sister chromatid exchanges in Chinese hamster ovary cells and of micronuclei and chromosomal aberrations in cultured human lymphocytes that were seen with lead chromate alone. However, nitrilotriacetic acid had no effect on the dose-related induction of sister chromatid exchanges in Chinese hamster ovary cells that was seen with potassium chromate alone. It was suggested that nitrilotriacetic acid increased the solubility of the originally insoluble lead chromate, leading to increased uptake of the metal cation by the cells and subsequent increased genotoxicity (Montaldi et al. 1987). Nitrilotriacetic acid increased the frequency of point mutations in *S. cerevisiae* observed with a low concentration of sodium chromate, but decreased the frequency with a 5-fold higher concentration of sodium chromate. It was suggested that at the low concentration of sodium chromate, nitrilotriacetic acid affected the uptake of chromium(VI), favoring reduction to chromium(III) ions, which formed a complex with nitrilotriacetic acid that can cross the membrane and interact with DNA. At the high dose of sodium chromate, nitrilotriacetic acid may have affected the mechanism of recombination repair of DNA breaks induced by chromate oxidizing activity (Bronzetti and Galli 1989). Nitrilotriacetic acid also increased the mutagenicity of potassium dichromate in *S. typhimurium* and *D. melanogaster*, presumably by favoring the reduction of chromium(VI) to chromium(III) (Gava et al. 1989a). Thus, it is possible that other hazardous substances at hazardous waste sites may be more dangerous due to the presence of chromium(VI).

Ascorbic acid has been shown to have a protective effect in rats administered lethal dermal doses of potassium dichromate (25 mg chromium(VI)/rat), and in preventing ulcerations of the skin (Samitz 1970). The nephrotoxicity due to subcutaneous injections of potassium chromate in rats was prevented by intramuscular administration of ascorbic acid (Powers et al. 1986). This occurred mainly through the reduction of chromium(VI) to the less toxic chromium(III) state. In cultured human bronchial cells, co-exposure to ascorbic acid and sodium chromate blocked chromate-induced clastogenicity by preventing uptake of chromium(VI) ions by cells (Wise et al. 2004). Vitamin E protected against, while vitamin B₂ enhanced, the cytotoxicity and DNA strand breaks induced by sodium chromate in Chinese hamster cells *in vitro*. Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991) (see Section 3.11.3). N-Acetylcysteine, the glutathione precursor, was reported to be effective in increasing the urinary excretion of chromium in rats (Nadig 1994).

Studies have examined the effects of interactions between chromium and arsenic on blood cholesterol and glucose levels and changes in organ weight in rats (Aguilar et al. 1997). Groups of five male Wistar rats were given food containing 5 µg/g of either arsenic(V) oxide, chromium(III) chloride, or a combination of

both chemicals for 10 weeks. Organ weight to body weight ratios of liver, spleen, lung, kidney, and heart were similar to control values for the three exposed groups. Arsenic alone increased the cholesterol blood level from 47.27(\pm 6.85 SD) mg/dL in the control group to 96.83(\pm 6.11 SD). The combination of arsenic and chromium reduced the blood cholesterol level to 46.69(\pm 6.11 SD) mg/dL. Neither chemical alone or in combination affected blood glucose levels. In most tissues, the combination of chemicals reduced the chromium level appreciably below control values. Supplemental chromium increased arsenic levels in liver, kidney, spleen, heart, and red blood cells, and reduced levels of arsenic in lung and hair tissues. Chromium did not appear to alter concentrations of arsenic in the liver.

A study examining the chromium(VI) reduction in microsomes noted that the level of iron in the test system markedly influenced the V_{\max} of chromium(VI) reduction, suggesting that coexposure to chromium(VI) and agents that increase intracellular iron might lead to increased risk for chromium(VI) toxicity (Myers and Myers 1998). Among chromium cement workers with severe and continuous hand dermatitis, the addition of ferrous sulfate to the cement reduced the total chromium body burden (Chou et al. 2008).

The effects of chromium(III) chloride and sodium chromate(VI) on the hepatotoxicity of carbon tetrachloride exposure to mouse hepatocytes were examined by Tezuka et al. (1995). Primary cultures of mouse hepatocytes were pretreated with 10 or 100 μ M chromium for 24 hours followed by exposure to 1–5 mM carbon tetrachloride for up to 1 hour. Chromium(VI) pretreatment significantly reduced the cell toxicity as well as lipid peroxidation caused by carbon tetrachloride. Chromium(III) pretreatment did not have any effect on cell toxicity. About 50% of chromium(VI) was taken up and reduced in the cells by 90% to chromium(III) within 10 minutes. The initial uptake rate of chromium(III) into cells was greater than 500-fold less than chromium(VI), and only about 5% was absorbed. The protection against carbon tetrachloride damage by chromium(VI) was attributed to its rapid uptake and conversion to chromium(III), and it was determined that chromium(III) acts as a radical scavenger for the free radicals generated by carbon tetrachloride within the cell. Furthermore, chromium(VI) pretreatment reduced the activity of NADPH cytochrome c reductase, which metabolizes carbon tetrachloride to reactive species. In a previous study (Tezuka et al. 1991), the same group found that pretreating mice and rats with chromium(III) also protected against hepatic toxicity.

In order to examine the speciation of chromium in lemonade, Kool Aid, tea, dripped coffee, percolated coffee, and orange juice, potassium chromate(VI) was added to each of the beverages at a chromium concentration of 10 mg/L (Kerger et al. 1996b). After 15 minutes, the concentrations of chromium(VI)

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were determined to be <0.4 mg/L for orange juice, <0.3 mg/L for coffee and tea, 2 mg/L for Kool Aid, and 0.3 mg/L for lemonade. After 3–5 hours, essentially no residual chromium(VI) remained. At higher concentrations (50 mg/L chromium(VI)), >99, 40, and 84% of the chromium(VI) was reduced after 3–5 hours in orange juice, lemonade, and coffee, respectively (not tested at the higher concentration in Kool Aid and tea). The reducing capacities were not correlated with total organic carbon or pH. The reducing capacities of the beverages were attributed in part to ascorbic acid in lemonade and orange juice and to tannins in tea and coffee.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chromium than will most persons exposed to the same level of chromium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of chromium, or compromised function of organs affected by chromium. Populations who are at greater risk due to their unusually high exposure to chromium are discussed in Section 6.7, Populations with Potentially High Exposures.

Acute inhalation LC₅₀ and oral and dermal LD₅₀ studies suggest that female animals are more sensitive to the lethal effects of chromium(VI) compounds (see Sections 3.2.1.1, 3.2.2.1, and 3.2.3.1). Whether human females are more sensitive than males to toxic effects of chromium or its compounds is not known. Other information identifying possible susceptible populations was not located. The primary and most sensitive effects of exposure to chromium compounds to the respiratory, gastrointestinal, hematological, and immunological systems; thus, individuals with preexisting conditions of these systems may be at increased risk of exposure to chromium compounds. Due to the sensitizing effects of chromium, some individuals who are sensitive to chromium may develop asthma as an anaphylactic response to inhaled chromium. Also, there is limited evidence that some individuals have less ability than others to reduce chromium(VI) in the bloodstream and are more likely to be affected by the adverse effects of chromium exposure (Korallus 1986a, 1986b). The ability to reduce chromium(VI) in the bloodstream may be related to the ascorbic levels in the plasma. However, the metabolic reduction of chromium(VI) may result in bioactivation and/or detoxification.

Since chronic inhalation of cigarette smoke may result in squamous metaplasia in the respiratory mucosa, the risk of lung cancer due to inhalation of carcinogenic chromium compounds may be exacerbated in individuals who smoke cigarettes or are excessively exposed to passive smoke (Albert 1991).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chromium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to chromium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to chromium:

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Chromium. In: Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Sanders Company, 794-795.

Leikin JB, Paloucek FP, eds. 2002. In: Leikin and Paloucek's poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 372-379.

Schonwald S. 2004. Chromium. In: Dart RC, ed. Medical toxicology. 3rd ed. Philadelphia, PA: Lippicott Williams & Wilkins, 1415-1417.

3.11.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of chromium following acute inhalation exposure have included moving the patient to fresh air, monitoring for respiratory distress, and administering humidified supplemental oxygen with assisted ventilation if required (Haddad et al. 1998; Schonwald 2004). If pulmonary effects such as bronchoconstriction are present, treatment with oxygen and bronchodilator drugs may be administered (Haddad et al. 1998). The absorption of inhaled chromium compounds depends on such factors as oxidation state, particle size, and solubility. Chromium(VI) passes through the alveolar lining of the lungs to the bloodstream more readily than does chromium(III) (see Section 3.4.1.1), and more soluble compounds are absorbed more readily than those that are less soluble (Bragt and van Dura 1983). Although chromium(VI) is more readily absorbed from the lungs than chromium(III), various components of the respiratory system can reduce chromium(VI) to chromium(III), which is far less capable of crossing cell membranes than chromium(VI), thereby reducing the bioavailability of chromium to target cells other than the lung (De Flora and Wetterhahn 1989). Epithelial lining fluid (ELF) is capable of reducing chromium(VI) (Petrilli et al. 1986b) and may represent the first line of defense against inhaled chromium(VI). Ascorbic acid (vitamin C) and glutathione, both of which were found to reduce chromium(VI) to chromium(III) in cell-free bronchoalveolar lavage fluid or soluble fractions of rat lungs *in vitro*, appear to be involved in this activity

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of ELF (Suzuki and Fukuda 1990). Uptake and reduction of chromium(VI) by pulmonary alveolar macrophages, catalyzed by NADH- or NADPH-dependent cytosolic enzyme activities, may lead to virtually irreversible sequestration and efficient removal by mucociliary action (De Flora and Wetterhahn 1989; De Flora et al. 1984, 1987b). Reduction of chromium(VI) within pulmonary alveolar macrophage homogenates was stimulated in rats by the administration of the glutathione precursor, N-acetylcysteine (De Flora and Wetterhahn 1989). As mentioned above, the reduction of chromium(VI) to chromium(III) by these various processes within the lungs serves as a natural defense mechanism by decreasing the amount of chromium absorbed and enhancing mucociliary clearance of chromium(III). However, reduction of chromium(VI) to chromium(III) generates reactive intermediates, which may produce adverse effects. Theoretically, further clearance from the lungs might be achieved by the administration of expectorants, but the efficacy of such a procedure has not been tested.

Chromium(III) is also poorly absorbed by the gastrointestinal tract, and chromium(VI) is reduced to chromium(III) in the gastric environment, limiting the bioavailability of chromium(VI) (De Flora et al. 1987a; Donaldson and Barreras 1966). Thus, the oral toxicity of chromium metal is low. However, chromium(VI) compounds are highly corrosive to the gastrointestinal tract and can lead to hepatic, renal, hematological, and neurological effects (Clochesy 1984; Coogan et al. 1991a; Diaz-Mayans et al. 1986; Iserson et al. 1983; Kaufman et al. 1970; Kumar and Rana 1982, 1984; Samitz 1970; Saryan and Reedy 1988). The reduction of chromium(VI) to chromium(III) in the stomach is greatly enhanced at low pH and shortly after meals due to increased gastric juice secretion (De Flora et al. 1987a). The enhanced reduction of chromium(VI) at low pH suggests that, theoretically, oral administration of bicarbonates and antacids should be avoided. Oral administration of ascorbic acid to further reduce chromium(VI) to chromium(III) might further decrease bioavailability (Haddad et al. 1998; Schonwald 2004), although this has not been proven (Leikin and Paloucek 2002; Schonwald 2004). Other recommendations for reducing gastrointestinal absorption of chromium include gastric lavage (Schonwald 2004); however, the approach would need to be performed shortly after ingestion and may be associated with risks (e.g., perforation). Inducing emesis with syrup of ipecac is not recommended because of the possibility of irritation or burns to the esophagus (Nadig 1994; Schonwald 2004).

In cases of dermal exposure, the skin should be thoroughly washed to prevent chromium absorption by the skin (Haddad et al. 1998; Leikin and Paloucek 2002; Schonwald 2004). As chromium(VI), but not chromium(III), is readily absorbed by the skin, ascorbic acid in the washing solution could reduce chromium(VI) to chromium(III), thus decreasing absorption. Application of the calcium disodium salt of ethylenediamine tetraacetic acid (EDTA), which acts as a chelating agent, has also been recommended

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after washing with water and application of ascorbic acid (Nadig 1994), especially in cases where the skin has been cut or abraded (Burrows 1983). Ascorbic acid was found to protect chromium-sensitive workers who handled chromates in the lithographing and printing industries from dermatitis. The ascorbic acid (10% solution) was kept near the work areas, and the workers soaked their hands and forearms as soon as possible after handling the chromate mixtures. In addition, ascorbic acid prevented ulcerations of the skin in rats treated with potassium dichromate dermally (Samitz 1970). An antichrome powder consisting of a mixture of 40% sodium metabisulfite, 20% ammonium chloride, 20% tartaric acid, and 20% sucrose as a 10% aqueous solution was effective in reducing the healing time of chrome sores on the skin of guinea pigs to which potassium dichromate had been applied (Samitz and Epstein 1962). Thorough irrigation with water has been recommended if the eyes have been exposed (Haddad et al. 1998; Schonwald 2004).

Both the cytotoxic effects of chromium(III) chloride, chromium(III) nitrate, sodium chromate(VI), sodium dichromate(VI), potassium dichromate(VI), and chromium(V) potassium sulfate dodecahydrate and the ability of ascorbic acid, glutathione 4-acetamido-4'-isothiocyano-2,2-stibenedisulphonic acid (SITS) to prevent chromium toxicity in transformed human keratinocytes were examined (Little et al. 1996). This cell line was used because histopathological studies have shown that dichromate compounds have caused keratinocyte necrosis. Cells were exposed to the chromium salts for 24 hours, and the viability of the cultures was examined for their ability to take up neutral red dye and release lactate dehydrogenase into the media. None of the chromium(III) or chromium(V) salts seemed toxic to the cells at concentrations up to about 100 μ M. The chromium(VI) salts showed toxicity at about 8 μ M, and there was little cell survival at 100 μ M. The dose-response curves were similar for all chromium(VI) salts tested. Similar experiments were conducted with normal human keratinocytes obtained from abdominoplasties or breast reductions from six donors and treated with sodium dichromate. The toxicity to normal cells overall seemed to be less than in the transformed line. Ascorbic acid at 500 μ M completely inhibited the cell toxicity caused by chromium(VI), whereas glutathione and SITS were less effective. Ascorbate probably protected cells by reducing chromium(VI) and chelation of the reduced complex. Glutathione may have formed complexes with the chromium(VI), which eventually led to chromium(III), whereas SITS may have inhibited the cellular uptake of the chromate by altering the nonspecific membrane anion carrier. The authors conclude that these available drugs provide protection against cytotoxicity to keratinocytes involved in dermatitis and may be useful to prevent toxic reactions to metals contacting the skin.

The effect of decreasing the concentration of water-soluble chromium in cement from about 10 to 2 ppm on the incidences of chromium-induced dermatitis was examined among construction workers in Finland

(Roto et al. 1996). After 1987, when the decrease occurred, allergic dermatitis caused by chromium in the industry was reduced by 33% from previous levels, whereas irritant contact dermatitis remained unchanged.

3.11.2 Reducing Body Burden

Once chromium has been absorbed, it can be widely distributed throughout the body (see Section 3.4.2). Forced diuresis with careful monitoring of fluid and electrolyte status has been suggested, but not proven, to increase the elimination of chromates (Haddad et al. 1998). In a case report of a fatality after ingestion of potassium chromate, hemodialysis and charcoal hemoperfusion did not significantly remove chromium from whole blood and had little effect on the management of chromium toxicity (Iserson et al. 1983). However, hemodialysis was effective in saving the life of an electroplater who accidentally swallowed plating fluid containing chromium trioxide (Fristedt et al. 1965). Because chromium may be sequestered in erythrocytes, exchange transfusion has been used as a way to decrease the body burden in serious acute poisoning (Kelly et al. 1982).

Both chromium(VI) and chromium(III) can be transported in the blood. Chromium(III) tends to bind to plasma proteins and is excreted in the urine. Chromium(VI) may be poorly reduced to chromium(III) in plasma, but this reduction can be enhanced by the intravenous administration of ascorbic acid (Korallus et al. 1984). However, reactions of chromium(VI) with sulfhydryl compounds or ascorbate may have mixed effects on toxicity, since such reactions yield reactive chromium intermediates, reactive oxygen species, and free cysteinyl and carbon radical species, which may be more damaging than chromium(VI) itself (Reynolds and Zhitkovich 2007; Shi et al. 1994; Stearns et al. 1994). Generally, treatments for reducing body burden of chromium are chelation therapies similar to those used to reduce body burdens of other metals, although the use of ascorbic acid is specific for chromium. Use of hemodialysis and N-acetylcysteine has been suggested to enhance elimination (Haddad et al. 1998; Leikin and Paloucek 2002; Schonwald 2004), however, this has not been proven. N-acetylcysteine, the glutathione precursor, was reported to be more effective than EDTA or dimercaptosuccinic acid in increasing the urinary excretion of chromium in rats (Banner et al. 1986; Nadig 1994); however, chelation with agents available in human clinical medicine, such as British Anti Lewisite (dimercaprol) and EDTA, has been shown to be generally ineffective in increasing the elimination of chromium (Ellis et al. 1982). However, calcium EDTA, administered intravenously, resulted in a rapid increase in the urinary excretion of chromium in metal workers (Sata et al. 1998). Other polyaminocarboxylic acid chelating agents may be effective in removing chromium from organs. In rats injected with potassium chromate, subsequent treatment with

various polyaminocarboxylic acid chelating agents resulted in significant removal of chromium from the liver, kidney, heart, or brain, depending on the agent. Ethylenediamine N,N'-diacetic acid (EDDA) removed significant amounts of chromium from the liver and heart. Ethylenediamine N,N'-di(O-hydroxyphenyl acetic acid (EDDHA) removed significant amounts of chromium from the kidney, heart, and brain. N-(2-hydroxyethyl)ethylenediamine triacetic acid (HEDTA) removed significant amounts of chromium from the liver and kidney. Hexamethylene 1,6-diamino N,N,N',N'-tetraacetic acid (HDTA) removed significant amounts of chromium from the liver, kidney, and brain. Triethylene tetramine N,N,N',N',N'',N''-hexaacetic acid (TTTHA) removed significant amounts of chromium from the liver. Ethyleneglycol-bis-(2-aminoethyl) tetraacetic acid (EGTA) did not remove significant amounts of chromium from any of the organs. The relative ability of the polyaminocarboxylic acids to remove chromium from organs may be related to the number of amino or carboxyl groups as complexing centers or by the presence of hydroxyl groups (Behari and Tandon 1980). The use of these agents in humans has not been tested. Chromium(VI), but not chromium(III), can readily cross cell membranes. Chromium(VI) readily enters erythrocytes, where it is reduced to chromium(III) by glutathione, and chromium(III) is essentially trapped within erythrocytes, where it binds to proteins, primarily hemoglobin. This may explain the fact that chromium shows little toxicity at sites distant from administration sites (De Flora and Wetterhahn 1989). The chromium(III) trapped within the erythrocytes would be released upon natural destruction of the erythrocyte and excreted in the urine.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium, whereas reduction of chromium(VI) outside of cells may be a major mechanism of protection. After entering target cells, chromium(VI) itself and/or the metabolically reduced valence states exert toxic effects, as discussed in detail below (De Flora and Wetterhahn 1989). Administration of a reducing agent (such as ascorbate) early enough after exposure to reduce chromium(VI) to chromium(III) in extracellular fluids before chromium(VI) penetrates cells may reduce toxicity; however, increased intracellular ascorbate may enhance toxicity. For example, in animal studies, ascorbic acid has been shown to protect against lethality of dermal potassium dichromate (Samitz 1970) and prevent nephrotoxicity of subcutaneously administered potassium chromate (Powers et al. 1986). However, increased intracellular ascorbate concentrations has been shown to enhance chromium(VI) toxicity in cultured human fibroblasts (Reynolds and Zhitkovich 2007). Therefore, agents that enhance reduction of chromium(VI) to chromium(III) may have mixed effects on toxicity. The effect of ascorbate or other reducing agents on chromium toxicity in humans has not been established.

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Once chromium enters the cell, ligand displacement and/or redox reactions of chromium(VI) with enzymes, proteins, and other molecules leads to reduction to chromium(V), chromium(IV), and chromium(III), with the generation of active oxygen species and radicals. The resulting toxicity depends on the nature of the cellular component that reacts with chromium(VI) and on the nature of the reactive species formed from the reaction. Chromium(VI) can be reduced metabolically by a number of cellular components under physiological conditions. Reduction by glutathione or cysteine can lead to generation of all valence states (particularly chromium(V)) and radicals. For example, *in vitro* reaction of chromium(VI) with glutathione led to the formation of glutathione thiyl radicals and chromium(V) complexes (Aiyar et al. 1991). Chromium(V)-glutathione complexes have been shown to form DNA adducts. Reduction by ascorbate leads to chromium(III), but chromium(V) has been generated by the reaction of chromium(VI) with riboflavin (vitamin B₂) and ribose derivatives (De Flora and Wetterhahn 1989). Reaction of chromium(VI) with hydrogen peroxide has led to the formation of chromium(V) complexes and hydroxyl radicals (Aiyar et al. 1991). Other important intracellular reduction reactions of chromium(VI) involve enzyme-catalyzed and NADPH-dependent mechanisms. Microsomal reduction of chromium(VI) by cytochrome P450 to chromium(III) may involve the transient formation of chromium(V) (De Flora and Wetterhahn 1989). Chromium(III), the final stable product of chromium(VI) reduction, can form chromium-DNA adducts and mediate crosslinking of DNA strands and DNA protein (De Flora and Wetterhahn 1989; Manning et al. 1992; Xu et al. 1996). Thus, the metabolic reduction of chromium(VI) may represent bioactivation and/or detoxification. If a bioactivation process, intracellular reduction of chromium(VI) would lead to the ultimate toxic species. Conversely, if chromium(VI) is the toxic agent, then effects would be elicited only if the amount of chromium(VI) entering target cells saturates the reducing mechanisms.

Differences in the intracellular metabolic pathways that result in the reduction of chromium(VI) will affect the nature of the reactive intermediates. For example, chelating ligands, such as glutathione and sugars, stabilize chromium(V) as an oxidation state, increasing its lifetime in the cell and ability to reach DNA in the nucleus. Cytochrome P450-dependent reduction of chromium(VI) to chromium(V) and chromium(IV), with generation of reactive radicals, which takes place in the endoplasmic reticulum, could occur in close enough proximity to the nuclear membrane and nonenzymatic reduction within the nucleus could occur in close enough proximity to chromatin for the transient intermediates to exert their effects, such as DNA strand breaks and radical-DNA adducts. As noted above, chromium(III) can form chromium-DNA adducts and mediate crosslinking of DNA strands and DNA protein (De Flora and Wetterhahn 1989).

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The role of glutathione in chromium-induced renal toxicity was investigated by Hojo and Satomi (1991). Male ddY mice (6 animals per dose group) were administered potassium dichromate(VI) (0.6 mmol chromium/kg), potassium tetraperoxochromate(V) (1.0 mmol/kg), green chromium(V)-glutathione complex (1.0 mmol/kg), and chromium nitrate(III) (0.6 mmol/kg); animals were sacrificed 24 hours after chromium injection and changes in kidney weight and function were assessed. Chromium(VI) resulted in a $10.7\% \pm 2.7$ decrease in body weight, a 2-fold increase in serum urea nitrogen, a decrease in kidney nonprotein sulfhydryl contents (3.3 ± 0.1 versus control values of 3.7 ± 0.1) and a decrease of kidney-glutathione reductase activity from a control value of 17.4 ± 1.5 to 14.1 ± 1.3 U/g. Potassium tetraperoxochromate(V) treatment resulted in 50% of the animals dying. Body weights and kidney-glutathione reductase activity were much lower than for animals treated with chromium(VI), and serum urea levels were 102.9 ± 17.7 mg/dL, which is about twice that observed in animals treated with chromium(VI). The chromium(V) glutathione complex was much less toxic and showed values that were similar or close to control values. Pretreatment with 10 mmol/kg glutathione methyl ester in the chromium(VI)-treated animals appeared to reduce the body weight loss and caused the serum urea levels to be normal. Butathione sulfoximine (an inhibitor of glutathione synthesis) greatly enhanced the levels of serum urea, loss of glutathione reductase activity and decrease in kidney nonprotein sulfhydryl groups. Butathione sulfoximine pretreatment resulted in one of the six animals dying. Animals treated with chromium(III) experienced weight loss, but other parameters were not markedly changed from control values. Pretreatment with butathione sulfoximine in animals treated with chromium(III) only caused a decrease in kidney nonprotein sulfhydryl groups. The authors indicated that with excess levels of glutathione, chromium(VI) is more readily reduced to chromium(III), whereas at lower levels of glutathione the reduction process is slower, resulting in slower reduction of the more toxic intermediate chromium(V). Also, at higher concentrations of glutathione, chromium(V)-glutathione complexes may form which may prevent chromium(V) from reacting at target sites that elicit toxic responses.

As discussed above, reactive intermediates formed during intracellular reduction of chromium(VI) to chromium(III) may interact with hydrogen peroxide, generating hydroxyl radicals, which can induce cell damage. Several animal and *in vitro* studies have assessed the effects of anti-oxidant agents on chromium-induced oxidative cell injury. Administration of folic acid, a free radical scavenger, to rabbits reduced potassium dichromate-induced increases in the concentration of free radical in liver, testes, brain, kidney, and lung and in serum liver enzyme activities of AST and ALT (El-Demerdash et al. 2006). Vitamin E, an antioxidant, has been shown to reduce potassium dichromate-induced renal toxicity and hepatotoxicity in rats (Appenroth et al. 2001; Arreola-Mendoza et al. 2006; Rao et al. 2006). Vitamin B₆,

which may have anti-oxidant potential due to its role as a co-factor in the synthesis of cysteine, reduced oxidative stress in the liver of rats exposed to potassium dichromate (Anand 2005). *In vitro* studies indicated that vitamin E protected against, while vitamin B₂ enhanced, the cytotoxicity and DNA single-strand breaks induced by sodium chromate in Chinese hamster cells. Formation of DNA-protein crosslinks by chromium(VI) in cell culture was prevented by addition of ascorbic acid (Capellmann et al. 1995), and ascorbic acid protected cells against chromosomal breakage and apoptosis. In rats, vitamin C was reported to prevent the effects of chromium(VI) on ovarian follicular development and the alterations in serum levels of estradiol, progesterone, and testosterone (Banu et al. 2008). Vitamin E also protected cells against chromosomal breaks (Blankenship et al. 1997) and decreased chromium(III)-induced oxidative damage to calf thymus DNA *in vitro*, as indicated by decreased formation of 8-hydroxydeoxyguanosine (Qi et al. 2000). Vitamin E may exert its protective effect by scavenging radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Selenium (as sodium selenate), an essential trace element, was protective of chromium(VI) toxicity in rat hearts (Soudani et al. 2011c). Selenium (as sodium selenate) also has been shown to reduce the genotoxicity of chromium dichromate in human lymphocytes *in vitro* as assessed by the Comet assay, although sodium selenite and selenous acid enhanced chromium-induced DNA damage; sodium selenate also decreased chromium-induced genotoxicity in *S. typhimurium* (strain TA102), as assessed by the Ames assay (Cemeli et al. 2003). Other vitamins or essential elements might also be effective in mitigating the effects of chromium by modulating the metabolic processes. The use of vitamins and essential elements for reducing the toxicity of chromium has not been studied in humans.

Thyroxine was found to ameliorate acute renal failure induced in rats by potassium dichromate, possibly by stimulating gluconeogenesis and Na-K ATPase activity in the renal cortex, influencing protein synthesis, and promoting glucose and amino acid uptake by epithelial cells. These events would be expected to aid in the repair and regeneration of the damaged tubular epithelial cells (Siegel et al. 1984). The use of thyroxine has not been tested in humans.

Todralazine, an antihypertensive drug, was found to markedly reduce the mutagenic activity of potassium dichromate(VI) in the bacterial tester strain TA100 and in the *B. subtilis* rec assay (Gasiorowski et al. 1997). Spectroanalysis indicated that chromium(VI) was reduced to chromium(III) by todralazine and that todralazine formed a complex with the chromium(III) ions. The reduction and complexing of chromium may have prevented chromium from crossing the membrane and may have prevented harmful interactions with DNA. Another study by this group found that complexing copper(II) chromate(VI) to organic ligands (e.g., 2-(2'-pyridyl)imidazole, 2,2'-bipyridyl, 1,10-phenanthroline) resulted in a decrease

in the mutagenicity of chromium(VI) as assessed by the Ames and *B. subtilis* rec assays (Gasiorowski et al. 1998).

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chromium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Chromium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chromium are summarized in [Figures 3-8](#) and [3-9](#). The purpose of these figures is to illustrate the existing information concerning the health effects of chromium. Each dot in the figures indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

A major source of oral exposure of humans to chromium is via the diet including chromium-rich diet supplements. Chromium(III) at low levels is essential to nutrition, and studies of chromium deficiency have been conducted. Information regarding health effects of exposure to chromium(VI) or chromium(III) in humans comes mainly from case reports of acute accidental or intentional ingestion,

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Figure 3-8. Existing Information on Health Effects of Chromium(VI)

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●		●	●	●	
Oral	●	●			●	●				●
Dermal	●	●	●	●	●					

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●		●	●	●		●	●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●			●					

Animal

● Existing Studies

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Figure 3-9. Existing Information on Health Effects of Chromium(III)

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation			●	●						●
Oral					●					
Dermal				●						

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●	●				●		
Oral	●		●	●		●	●	●		●
Dermal		●			●					

Animal

● Existing Studies

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acute accidental dermal exposure, and from occupational case reports and epidemiology studies, which primarily involve inhalation and dermal exposure. In occupational studies, it is often difficult to separate exposure to chromium(VI) from chromium(III). Case reports have shown that ingestion and dermal contact with chromium(VI) can cause death. These reports have also described the serious systemic and neurological sequelae of exposure leading to death. Occupational exposures to chromium(VI) and/or chromium(III) are associated with respiratory and nasal, cardiovascular, gastrointestinal, hematological, hepatic, renal, and dermal effects. Immunological effects in humans exposed by inhalation and dermal contact consist of sensitization resulting in asthma and contact dermatitis, which can be exacerbated by oral exposure. Limited information was available regarding reproductive effects of occupational exposure to chromium(VI). Limited information was found on neurological behavioral effects.

Information is also available regarding genotoxic effects in workers exposed to chromium(VI) and cancer in workers exposed to chromium(VI) and/or chromium(III).

Information regarding the levels of exposure to chromium(VI) compounds that cause death in animals is available for the inhalation, oral, and dermal routes. Information regarding respiratory effects of acute inhalation exposure of animals to chromium(VI) was available. Acute oral studies have evaluated effects of chromium(VI) on hematology and clinical chemistry. Acute dermal exposure of animals to chromium(VI) can cause irritation, edema, necrosis, and chrome sores. Information on systemic effects of chromium(VI) in animals is available for intermediate- and chronic-duration exposure by the inhalation route. Information regarding effects of oral exposure is available for intermediate and chronic durations. The immunological effects of chromium(VI) in animals have been studied after inhalation and dermal exposure. An inhalation study reported no developmental or reproductive effects of chromium(VI). The reproductive and developmental effects of oral chromium(VI) have been evaluated following oral exposure, showing adverse effects, particularly to the male reproductive system. Information regarding the genotoxicity and carcinogenicity of chromium(VI) is available for both the inhalation and oral routes.

Information regarding levels of chromium(III) compounds that result in death is available only for the oral route. Systemic effects of acute-duration exposure to chromium(III) are limited to the respiratory system- and intermediate-duration inhalation exposure to chromium(III) are limited to the respiratory system. Information on systemic effects of chronic inhalation exposure to chromium(III) is limited to a study that used a mixture of chromium(VI) and chromium(III). Studies of intermediate- and chronic duration oral exposure to chromium(III) failed to find any systemic, neurological, developmental, reproductive, or carcinogenic effects. The immunological and genotoxic effects of chromium(III) in

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animals have not been tested by the oral route. Information regarding effects of dermal exposure of animals to chromium(III) is limited to a study of skin ulceration after acute exposure and dermal sensitization tests. One report of chronic renal failure after ingestion of over-the-counter chromium picolinate at 0.6 mg/day was found in literature (Wasser et al. 1997).

In addition to the information on chromium(VI) and chromium(III), limited information is available regarding health effects of chromium(0) and chromium(IV). Briefly, the available information on chromium(0) consists of studies that examined workers at an alloy steel plant (Triebig et al. 1987) and boilermakers (Verschoor et al. 1988) for possible renal effects. Information on chromium(IV) consists of a 2-year inhalation study of chromium dioxide in rats that found no effects upon hematological, clinical chemistry, and urinalysis parameters and no histopathological effects on respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal/ocular, neurological, and reproductive organs (Lee et al. 1989).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure of humans to chromium(VI) as occurs in occupational settings can result in respiratory irritation (dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation), dizziness, and headache at high concentrations, and can trigger asthmatic attacks in sensitized individuals (Lieberman 1941; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989). High airborne levels of chromium(VI) can also cause gastrointestinal irritation (Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950). Information on toxic effects in humans after oral exposure to chromium(VI) is limited to case reports of humans who ingested lethal or near lethal doses. Serious respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological effects have been described as sequelae leading to death (Clochesy 1984; Iserson et al. 1983; Kaufman et al. 1970; Saryan and Reedy 1988). Acute dermal exposure can cause skin burns and can also have similar sequelae that lead to death (Brieger 1920; Major 1922). No information regarding systemic effects of acute inhalation exposure of animals to chromium(VI) was located. Information regarding effects of acute oral exposure of animals to chromium(VI) include a report of gastrointestinal hemorrhage in rats given a lethal dose of potassium dichromate (Samitz 1970), evaluations of hematology and clinical chemistry parameters in rats and mice exposed for 4–5 days (NTP 2007, 2008a) and increased resorptions in mice given potassium dichromate during gestation (Junaid et al. 1996b). Information regarding effects of acute dermal exposure of animals to chromium(VI) is limited to studies of dermal irritation and sensitization (Gad et al. 1986; Merkur'eva et al. 1982; Samitz 1970; Samitz and Epstein 1962). The information in humans indicates that many organs can be targets of acute exposure to chromium(VI) if exposure levels

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are high enough. Studies in animals show that hematological effects occur following acute oral exposure and may be the earliest indication of more severe adverse effects observed following longer duration exposures. No information was located regarding systemic effects in humans after acute exposure to chromium(III) compounds by any route. Acute inhalation studies of chromium trichloride in hamsters (Henderson et al. 1979) and chromic oxide and basic chromium sulfate in rats (Derelanko et al. 1999) indicated that the respiratory system is also a target of chromium(III) exposure. Acute dermal studies show that chromium(III) can be a sensitizer, and that dermal challenge of sensitized individuals with chromium(III) compounds can elicit a response (Hansen et al. 2003; Samitz and Epstein 1962). LD₅₀ values for chromium(VI) and chromium(III) compounds indicate that chromium(III) is less toxic than chromium(VI) (Shubochkin and Pokhodzie 1980; Smyth et al. 1969; Vernot et al. 1977).

Additional studies involving acute exposure to both chromium(VI) and chromium(III) compounds by all routes would be helpful, especially if they evaluated comprehensive toxicological end points and exposure-response relationships. Studies defining the possible synergistic effects of chromium with other nephrotoxins, such as mercury and cadmium, which may be stored together at toxic waste sites, would also be useful. There are populations surrounding hazardous waste sites that might be exposed to the substance for short periods; therefore, this information is important.

Intermediate-Duration Exposure. There are no studies regarding systemic effects in humans after oral exposure of intermediate duration to either chromium(VI) or chromium(III). Intermediate-duration exposure to primarily chromium(VI) in occupational studies caused nasal and respiratory effects (Bovet et al. 1977; Davies et al. 1991; Gomes 1972; Kleinfeld and Rosso 1965; Lee and Goh 1988; Sorahan et al. 1987; Taylor 1966). Intermediate-duration exposure in occupational settings involving dermal exposure also can cause chrome ulcers or holes in the skin (Gomes 1972; Lee and Goh 1988; Lieberman 1941; PHS 1953; Smith 1931). An MRL of 5×10^{-6} mg chromium(VI)/m³ has been determined for upper respiratory effects in humans after intermediate-duration inhalation exposure to chromium(VI) as chromium(VI) trioxide mist and other hexavalent chromium mists and dissolved aerosols, based on the study by Lindberg and Hedenstierna (1983).

The respiratory tract and the immune system are targets in animals exposed to chromium(VI) and chromium(III) via inhalation for intermediate durations (Adachi 1987; Adachi et al. 1986; Glaser et al. 1985, 1990; Johansson et al. 1986a, 1986b), with LOAEL values identified for respiratory and immune effects after inhalation (Glaser et al. 1985, 1990). An MRL of 0.0003 mg chromium(VI)/m³ has been determined for lower respiratory effects in humans after intermediate-duration inhalation exposure to

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chromium(VI) as particulate hexavalent compounds based on the study in rats by Glaser et al. (1990). An intermediate-duration study on chromium(III) compounds in rats identified respiratory system as the target for inhaled insoluble chromic oxide and soluble basic chromium sulfate (Derelanko et al. 1999). Based on differences in respiratory effects of these two compounds, distinct intermediate-duration MRLs were derived for insoluble and soluble trivalent chromium compounds. The minimal LOAEL of 3 mg chromium(III)/m³ for septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats exposed to chromic oxide was used to derive the intermediate-duration inhalation MRL of 0.005 mg chromium(III)/m³ for insoluble trivalent chromium compounds. The LOAEL of 3 mg chromium(III)/m³ for lesions of the larynx (granulomatous inflammation) and nose (inflammation) in female rats exposed to basic chromium sulfate was used to derive the intermediate-duration inhalation MRL of 0.0001 mg chromium(III)/m³ for soluble trivalent chromium compounds.

The gastrointestinal and hematological systems were identified as the primary targets of intermediate-duration oral exposure of rats and mice exposed to chromium(VI) in drinking water (NTP 2007, 2008a). An intermediate-duration oral MRL of 0.005 mg chromium(VI)/kg/day has been determined for hematological effects (e.g., microcytic, hypochromic anemia) in rats after intermediate-duration oral exposure to chromium(VI) as sodium dichromate dihydrate in drinking water in a study by NTP (2008a). In addition, developmental and reproductive studies identify chromium(VI) as a reproductive and developmental toxicant in monkey, rats, and mice after oral exposure (Al-Hamood et al. 1998; Aruldas et al. 2004, 2005, 2006; Bataineh et al. 1997; Chowdhury and Mitra 1995; Junaid et al. 1996b; Kanojia et al. 1996, 1998; Subramanian et al. 2006; Trivedi et al. 1989; Yousef et al. 2006; Zahid et al. 1990). Oral studies of intermediate-duration in rats and mice reported no effects of chromium(III) in any system (Ivankovic and Preussmann 1975; NTP 2008b; Shara et al. 2005). Adverse reproductive effects were observed following oral exposure to chromium(III), although NOAEL values were not established. No dermal studies of intermediate duration in animals were located. The toxicity of intermediate-duration exposure to chromium compounds is relatively well characterized for the oral and inhalation routes. Dermal studies would be useful to determine possible target organs other than the skin. There are populations surrounding hazardous waste sites that might be exposed to the substance for similar durations.

Chronic-Duration Exposure and Cancer. The respiratory system (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gibb et al. 2000a; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Kuo et al. 1997a; Letterer 1939; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989; Sassi 1956; Sluis-Cremer and du Toit

1968; Sorahan et al. 1987; Taylor 1966) and the skin (Gomes 1972; Hanslian et al. 1967; Lee and Goh 1988; Lieberman 1941; PHS 1953; Royle 1975b) are the primary target organs for occupational exposure to chromium and its compounds. An MRL of 5×10^{-6} mg chromium(VI)/m³ has been determined for upper respiratory effects in humans after chronic-duration inhalation exposure to chromium(VI) as chromium(VI) trioxide mist and other hexavalent chromium mists and dissolved aerosols, based on the study by Lindberg and Hedenstierna (1983). There are more data regarding the effects of chronic inhalation exposure in humans and animals than there are regarding the effects of oral exposure. Studies of populations residing in areas contaminated with chromium(VI) in China have found such effects as oral ulcer, diarrhea, abdominal pain, indigestion, vomiting, constipation, nose and eye irritation, headache, fatigue, dizziness, and leukocytosis (Zhang and Li 1987). Chronic inhalation studies with rats, mice, guinea pigs, and rabbits also identify the respiratory system as the main target of chromium(VI) and chromium(III) exposure (Glaser et al. 1986, 1988; Nettesheim and Szakal 1972; Steffee and Baetjer 1965). Chronic oral exposure studies in rats and mice exposed to chromium(VI) in drinking water identify the hematological and gastrointestinal systems as the primary targets of chronic oral exposure (NTP 2008a), with gastrointestinal effects more sensitive than hematological effects. A chronic-duration oral MRL of 0.0009 mg chromium(VI)/kg/day based on gastrointestinal effects (diffuse epithelial hyperplasia of the duodenum) was derived for hexavalent chromium compounds. Chronic oral exposure to chromium(III) compounds did not result in any target organ toxicity in animals (Ivankovic and Preussmann 1975; MacKenzie et al. 1958; NTP 2008b; Schroeder et al. 1965; Shara et al. 2007); thus, no chronic-duration MRL was derived for chromium(III) compounds since target organs have not been identified and no NOAEL for reproductive effects of oral exposures has been adequately characterized. As noted above, the skin is a sensitive target of toxicity in workers exposed to airborne chromium (the effects resulted from direct dermal contact with chromium). No chronic dermal studies in animals were located. Because water and soil sources can be contaminated near hazardous waste sites, more information regarding chronic oral or dermal exposure would be useful.

Cancer. Occupational and environmental epidemiological studies indicate a correlation between long-term exposure to chromium(VI) compounds and lung cancer (Alderson et al. 1981; Baetjer 1950; Bidstrup 1951; Bidstrup and Case 1956; Braver et al. 1985; Cole and Rodu 2005; Crump et al. 2003; Dalager et al. 1980; Davies 1979, 1984; Davies et al. 1991; EEH 1976, 1983; Enterline 1974; Franchini et al. 1983; Frentzel-Beyme 1983; Gibb et al. 2000b; Goldbohm et al. 2006; Haguenoer et al. 1981; Hayes et al. 1979, 1989; Korallus et al. 1982; Langård and Norseth 1975; Langård and Vigander 1983; Langård et al. 1980; Machle and Gregorius 1948; Mancuso 1975, 1997a; Mancuso and Hueper 1951; Ohsaki et al. 1978; Park and Stayner 2006; Park et al. 2004; Pastides et al. 1994; PHS 1953; Rosenman and Stanbury

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1996; Sassi 1956; Satoh et al. 1981; Sheffet et al. 1982; Silverstein et al. 1981; Sjogren et al. 1987; Sorahan et al. 1987; Taylor 1966; Zhang and Li 1987). Occupational studies generally consider inhalation exposures, while environmental studies involve exposure by inhalation, ingestion, and dermal contact. Additional studies on populations exposed to chromium in drinking water would be useful to determine if a causal relationship with cancer exists. A unit risk for cancer from inhalation exposure to chromium(VI) compounds has been derived (IRIS 2008) from an occupational study (Mancuso 1975). Chronic inhalation of chromium(VI) compounds was carcinogenic in rats (Glaser et al. 1986) and mice (Nettesheim et al. 1971), and the 2-year carcinogenicity study on oral chromium(VI) provided clear evidence of oral cancers in rats and gastrointestinal cancers in mice (NTP 2008a). Cancer studies by parenteral route support the conclusions that chromium(VI) is carcinogenic (Furst et al. 1976; Hueper 1955, 1958; Hueper and Payne 1959, 1962; Laskin et al. 1970; Levy et al. 1986; Roe and Carter 1969; Steinhoff et al. 1986). For chromium(III) compounds, evidence for carcinogenesis (preputial adenomas in male rats) in the NTP (2008b) 2-year bioassay was equivocal. The available human and animal data are sufficient for determining that chromium(VI) is carcinogenic following inhalation and oral exposure. However, additional animal studies are needed to adequately assess the carcinogenic potential of chromium(III) following inhalation and oral exposure.

Genotoxicity. Several studies evaluating chromosomal aberrations, sister chromatid exchange, micronuclei, DNA strand breaks and DNA-protein crosslinks in workers exposed to chromium(VI) have been conducted, some reporting positive results (Benova et al. 2002; Deng et al. 1988; Gambelunghe et al. 2003; Koshi et al. 1984; Lai et al. 1998; Medeiros et al. 2003a; Sarto et al. 1982; Stella et al. 1982; Vaglenov et al. 1999; Werfel et al. 1998; Wu et al. 2001) and some reporting negative results (Benova et al. 2002; Gao et al. 1994; Hamamy et al. 1987; Husgafvel-Pursiainen et al. 1982; Littorin et al. 1983; Medeiros et al. 2003a; Nagaya 1986; Nagaya et al. 1991). However, most of these studies are limited by factors such as lack of exposure data, co-exposure to other potentially genotoxic agents, and too few workers for meaningful statistical analysis. Mostly positive results have been found in rodents and *D. melanogaster* exposed to chromium(VI) compounds *in vivo* (De Flora et al. 2006; Gava et al. 1989a; Itoh and Shimada 1993; Kaya et al. 2002; Kirpnick-Sobol et al. 2006; Mirsalis et al. 1996; NTP 2007; Olvera et al. 1993; Paschin et al. 1982; Rasmuson 1985; Rodriguez-Arnaiz and Martinez 1986; Sarkar et al. 1993; Shindo et al. 1989; Tsapakos et al. 1983b; Ueno et al. 2001; Wang et al. 2006; Wild 1978; Zimmering et al. 1985). Numerous *in vitro* genotoxicity studies have been conducted in bacteria (Bennicelli et al. 1983; De Flora 1978, 1981; Haworth et al. 1983; Kanematsu et al. 1980; Kortenkamp et al. 1996b; Llagostera et al. 1986; Nakamuro et al. 1978; Nishioka 1975; NTP 2007; Olivier and Marzin 1987; Tagliari et al. 2004; Venier et al. 1982; Venitt and Levy 1974; Watanabe et al. 1998a; Yamamoto et

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al. 2002), yeast (Bonatti et al. 1976; Fukunaga et al. 1982; Kirpnick-Sobol et al. 2006; Singh 1983), cultured animal cell systems (Briggs and Briggs 1988; DiPaolo and Casto 1979; Douglas et al. 1980; Elias et al. 1989b; Fornace et al. 1981; Kowalski et al. 1996; Levis and Majone 1979; MacRae et al. 1979; Montaldi et al. 1987; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Seoane and Dulout 1999; Sugiyama et al. 1986a; Tsuda and Kato 1977; Ueno et al. 1995a; Umeda and Nishimura 1979; Venier et al. 1982; Wise et al. 1993; Yang et al. 1992), and human cell systems (Blasiak and Kowalik 2000; Depault et al. 2006; Douglas et al. 1980; Fornace et al. 1981; Gomez-Arroyo et al. 1981; Ha et al. 2004, 2004; Holmes et al. 2006; MacRae et al. 1979; Montaldi et al. 1987; Nakamuro et al. 1978; Sarto et al. 1980; Stella et al. 1982; Sugiyama et al. 1986a; Trzeciak et al. 2000; Whiting et al. 1979; Wise et al. 2002, 2004, 2006a, 2006b), mostly with positive results. The vast majority of studies, therefore, clearly indicated that chromium(VI) compounds are genotoxic.

Genotoxicity data are also available for chromium(III) compounds. A study in tannery workers, who were exposed mainly to chromium(III), reported negative results for chromosomal aberrations and sister chromatid exchange (Hamamy et al. 1987), while positive results for micronuclei and DNA-protein crosslinks were reported in another study on tannery workers (Medeiros et al. 2003a). Chromium trichloride, chromium picolinate, and niacin-bound chromium(III) also did not cause DNA damage, or increased frequencies of micronuclei in rats exposed *in vivo* (Cupo and Wetterhahn 1985; De Flora et al. 2006; NTP 2008b; Shara et al. 2005). Transplacental exposure to chromium(III) chloride salt resulted in DNA deletions (Kirpnick-Sobol et al. 2006). Mostly negative results have been found in *in vitro* genotoxicity studies of chromium(III) compounds in bacteria (Bennicelli et al. 1983; De Flora 1981; Kanematsu et al. 1980; Llagostera et al. 1986; Matsui 1980; Nishioka 1975; NTP 2008b; Olivier and Marzin 1987; Petrilli and De Flora 1978b; Shara et al. 2005; Venier et al. 1982, 1989; Yamamoto et al. 2002), and mammalian cell systems (Fornace et al. 1981; Itoh and Shimada 1996; Le Curieux et al. 1992; Levis and Majone 1979; MacRae et al. 1979; Newbold et al. 1979; Ohno et al. 1982; Raffetto et al. 1977; Sarkar et al. 1993; Sarto et al. 1980; Shara et al. 2005; Stella et al. 1982; Tsuda and Kato 1977; Ueno et al. 1995a; Umeda and Nishimura 1979; Whiting et al. 1979; Wise et al. 1993; Yang et al. 1992). Chromium(III) did not increase the number of micronuclei in polychromatic erythrocytes in mice (Itoh and Shimada 1996). Several studies have found weakly positive or positive results in Chinese hamster ovary cells (Coryell and Stearns 2006; Levis and Majone 1979; Stearns et al. 2002), mouse fetal cells (Raffetto et al. 1977), mouse lymphoma cells (Whittaker et al. 2005), and human cell lines (Blasiak and Kowalik 2000; Nakamuro et al. 1978; Stella et al. 1982).

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Chromium(III) compounds are less genotoxic than chromium(VI) compounds in intact cell systems because of the relative inability of chromium(III) to cross cell membranes; however, chromium(III) is more genotoxic than chromium(VI) when tested *in vitro* in subcellular targets (Kowalski et al. 1996; Snow 1991; Snow and Xu 1989). The reduction of chromium(VI) to chromium(III) as the ultimate genotoxicant within cells may account for the genotoxicity of chromium(VI) (Beyersmann and Koster 1987). However, in intact cells, chromium(III) appears less genotoxic than chromium(VI) due to decreased cellular permeability to chromium(III).

Additional studies in workers with known levels of chromium exposure that control for confounding factors would be useful for defining levels at which chromosomal aberrations occur in humans exposed to chromium(VI) in the workplace. Also, better dose-response relationships would be useful for the various genotoxic and regulatory effects observed with chromium to better determine which end points are the most sensitive and dominant at exposures near environmental levels.

Reproductive Toxicity. No reliable information was located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to chromium or its compounds. Studies in women exposed occupationally also show that chromium can be transferred to fetuses through the placenta (Shmitova 1980). Inhalation studies would be useful for determining the reproductive toxicity of inhaled chromium and compounds and for establishing exposure-response relationships. Adverse effects on the male reproductive system (included decreased spermatogenesis and histopathological alterations to the epididymis) were observed in monkeys exposed to chromium(VI) in drinking water for 180 days (Aruldas et al. 2004, 2005, 2006; Subramanian et al. 2006). Effects on spermatogenesis were reported in male rats given chromium(VI) by gavage for 90 days (Chowdhury and Mitra 1995) and in rabbits exposed to chromium(VI) in drinking water for 10 weeks (Yousef et al. 2006). In male mice, oral exposure of intermediate duration to chromium(VI) or chromium(III) was reported to result in decreased spermatogenesis and cellular degeneration of the outer layer of seminiferous tubules (Zahid et al. 1990); alterations in testicular, seminal vesicle, and preputial gland weights and decreased fertility were observed in mice following intermediate-duration exposure to chromium(VI) or chromium(III) (Elbetieha and Al-Hamood 1997). However, results of the study by Elbetieha and Al-Hamood 1997 should be interpreted with caution due to concern regarding experimental methods (see discussion in Section 2.3, Minimal Risk Levels). But other studies found no reproductive effects in male or female mice (NTP 1996a, 1996b, 1997, 2007, 2008a) exposed to chromium(VI) or chromium(III) (NTP 2008b; Shara et al. 2005, 2007). Alterations in sexual behavior and aggressive behavior toward other males were observed in male rats exposed to chromium(VI) or chromium(III) (Bataineh et al. 1997). Female mice or rats exposed orally to

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chromium(VI) compounds prior to mating (Junaid et al. 1996a; Kanojia et al. 1996, 1998) or female mice exposed during gestation (Junaid et al. 1996b; Trivedi et al. 1989) had increased fetal resorptions and decreased litter size. Alterations in ovarian and uterine weights and impaired fertility were observed in female mice that were exposed to chromium(III) or chromium(VI) and then were mated with unexposed mice (Elbetieha and Al-Hamood 1997); however, these results should be interpreted with caution due to concern regarding experimental methods (see discussion in Section 2.3, Minimal Risk Levels). Reductions in numbers of follicles and ova/mouse were seen following oral chromium(III) exposure (Murthy et al. 1996). Impaired development of the reproductive system was observed in the female offspring of mice exposed to potassium dichromate(VI) or chromium(III) chloride (Al-Hamood et al. 1998). A decrease in the number of pregnancies was observed in female rats administered 33.6 mg chromium(III)/kg/day as chromium chloride (by gavage) on gestational days 1–3; the same treatment on gestational days 4–6 did not alter the number of pregnancies (Bataineh et al. 2007). Distribution studies in pregnant rats given chromium(VI) or chromium(III) orally (Mertz et al. 1969) or intravenously (Danielsson et al. 1982) and in pregnant mice given chromium(III) intraperitoneally (Iijima et al. 1983) indicated that chromium can cross the placenta after administration of either valence state. The available data on reproductive effects of chromium and its compounds are inadequate for establishing dose relationships; thus, further studies to establish the LOAEL and NOAEL values would be valuable. No dermal toxicity studies examining reproductive end points were identified; dermal studies would be useful for assessing the reproductive toxicity of chromium and compounds following dermal contact and for establishing exposure-response relationships.

Developmental Toxicity. No reliable information was located regarding developmental toxicity in humans after inhalation, oral, or dermal exposure or in animals after dermal exposure to chromium or its compounds. A study in women exposed occupationally reported that chromium can be transferred to fetuses through the placenta (Shmitova 1980), but the poor quality and reporting of this study preclude its use for drawing conclusions regarding potential developmental effects of chromium in humans. In female rats and mice, oral exposure of acute or intermediate duration to chromium(VI) compounds resulted in fetal toxicity (Elsaieed and Nada 2002; Junaid et al. 1996a, 1996b; Kanojia et al. 1996, 1998; Trivedi et al. 1989), but a NOAEL for these effects was not identified. Chromium(VI) delayed the onset of puberty in rats (Banu et al. 2008; Samuel et al. 2011). Chromium(VI) also decreased antioxidant enzyme activity in the liver, kidney, and bone of neonatal rats born to dams exposed during gestation and lactation (Soudani et al. 2010b, 2011a, 2011b). Impaired development of the reproductive system was observed in the female offspring of mice exposed to potassium dichromate(VI) or chromium(III) chloride (Al-Hamood et al. 1998). Distribution studies in rat dams given chromium(VI) or chromium(III)

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intravenously (Danielsson et al. 1982) or orally (Mertz et al. 1969) and in mouse dams given chromium(III) intraperitoneally (Iijima et al. 1983) indicated that chromium can cross the placenta after administration of either valence state. No developmental effects were observed in the offspring of rats fed 1,806 mg chromium(III)/kg/day as chromium oxide for 60 days before mating and throughout the gestational period (Ivankovic and Preussmann 1975). No pharmacokinetic studies have been conducted regarding the distribution of chromium or its compounds to the fetus after inhalation or dermal exposure of the dams. Further oral developmental studies of chromium(VI) and chromium(III) in mice and other species would be useful to determine a NOAEL. These studies should include examination of developmental/neural end points. Developmental studies using inhalation exposure would be useful to determine if developmental effects are route specific. Data from oral, inhalation and dermal studies would be useful for determining dose-response relationships.

Immunotoxicity. In humans, allergic sensitization, characterized by asthma attacks and dermatitis, has been reported after occupational inhalation or occupational dermal exposure (Keskinen et al. 1980; Leroyer et al. 1998; Moller et al. 1986; Olaguibel and Basomba 1989) or dermal exposure (Burrows 1983; Engel and Calnan 1963; Engebrigtsen 1952; Eun and Marks 1990; Fregert 1975; Hansen et al. 2003; Kaplan and Zeligman 1962; Levin et al. 1959; Nethercott et al. 1994; Newhouse 1963; Peltonen and Fraki 1983; Samitz and Shrager 1966; Wahba and Cohen 1979; Winder and Carmody 2002; Winston and Walsh 1951) to chromium compounds. Two occupational studies suggest that chromium exposure affects the leukocyte populations in the blood of workers (Boscolo et al. 1997; Mancuso 1951). Delayed anaphylactoid reaction was observed in one case (Moller et al. 1986). Dermatitis was exacerbated in sensitized individuals by oral exposure to chromium(VI) (Goitre et al. 1982; Kaaber and Veien 1977).

In rats, nonspecific disease resistance mechanisms of the lung are inhibited by inhalation exposure to chromium and its compounds (Glaser et al. 1985). Inhalation exposure of intermediate duration alters immunoglobulin levels, lymphocyte responses to antigen and lectin, and spleen weight in rats (Glaser et al. 1985), as well as altered numbers of total recoverable cells, neutrophils, and monocytes, and percentages of pulmonary macrophages in bronchopulmonary lavage (Cohen et al. 1998). Intermediate-duration oral exposure of rats to chromium(VI) increased the proliferative response of T- and B-lymphocytes to mitogens and antigens (Snyder and Valle 1991).

There are sufficient data to determine that chromium or its compounds affect the immune system. More sensitive tests of the immune function after inhalation, oral, or dermal exposure to chromium or its compounds would be useful to determine the threshold levels for effects in humans. Studies evaluating

exposure levels required to produce sensitization and elicitation of allergic responses would also provide additional information regarding threshold levels. Additional studies that explore changes in cytokine levels (Snyder et al. 1996) caused by chromium exposure should prove helpful since they may provide mechanistic information as to how chromium may affect immune function.

Neurotoxicity. Exposure of humans to high levels of airborne chromium(VI) in occupational and environmental settings produced symptoms of dizziness, headache, and weakness (Lieberman 1941). Cerebral edema was found in a case of fatal poisoning by ingestion (Kaufman et al. 1970). No studies were located describing neurotoxic effects in animals after inhalation and dermal exposure to chromium or its compounds. A 28-day drinking water study in rats reported decreased motor activity and ponderal balance, although a complete battery of neurological function tests was not conducted (Diaz-Mayans et al. 1986). Some distribution studies have detected chromium in the brain (Behari and Tandon 1980; Danielsson et al. 1982; Kaufman et al. 1970; Tandon et al. 1979). More recently, patients with 8–25-fold higher chromium blood levels that resulted from parenteral feeding did not have increased signs of somatopsychic responses (Lovrinevic et al. 1996). However, the number of patients studied was small and they were suffering from serious clinical diseases.

Since the central nervous system may be a target organ for exposure to chromium or its compounds, additional inhalation, oral, and dermal studies would be useful to corroborate the limited data and would provide useful information for populations near hazardous waste sites. More information on people (adults, children) environmentally exposed to chromium would be useful to assess its potential to effect neuro/behavioral end points.

Epidemiological and Human Dosimetry Studies. Most epidemiology studies use cohorts of occupationally exposed individuals and provide consistent data indicating that inhaled chromium can be carcinogenic (Alderson et al. 1981; Baetjer 1950; Bidstrup 1951; Bidstrup and Case 1956; Braver et al. 1985; Cole and Rodu 2005; Crump et al. 2003; Cruz et al. 2006; Dalager et al. 1980; Davies 1979, 1984; Davies et al. 1991; EEH 1976, 1983; Enterline 1974; Fernandez-Nieto et al. 2006; Franchini et al. 1983; Frentzel-Beyme 1983; Gibb et al. 2000b; Goldbohm et al. 2006; Haguenoer et al. 1981; Hayes et al. 1979, 1989; Korallus et al. 1982; Langård and Norseth 1975; Langård and Vigander 1983; Langård et al. 1980; Machle and Gregorius 1948; Mancuso 1975, 1997a; Mancuso and Hueper 1951; Ohsaki et al. 1978; Park and Stayner 2006; Park et al. 2004; Pastides et al. 1994; PHS 1953; Rosenman and Stanbury 1996; Sassi 1956; Satoh et al. 1981; Sheffet et al. 1982; Silverstein et al. 1981; Sjogren et al. 1987; Sorahan et al. 1987; Taylor 1966) and can cause other toxic effects such as respiratory irritation, nasal septum

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perforation, and chrome sores on the skin (due to dermal exposure) (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gibb et al. 2000a; Gomes 1972; Hanslian et al. 1967; Keskinen et al. 1980; Kitamura et al. 2003; Kleinfeld and Rosso 1965; Lee and Goh 1988; Lieberman 1941; Letterer 1939; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Olaguibel and Basomba 1989; Osim et al. 1999; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966). Results of epidemiological data are consistent with results of studies in experimental animals showing that the lung is the target organ for inhaled chromium(VI). Epidemiology studies in the chromate production industry and in chrome pigment manufacture and chrome plating have consistently shown an association with increased risk of lung cancer, but studies in other industries, such as stainless steel welding, electroplating, and ferrochromium production, have yielded inconclusive results. Exposure to chromium(VI) in these industries is associated with these effects, but the case for chromium(III) is less clear. Further studies in these industries may lead to more conclusive results. Measurements of chromium in urine and blood are useful for monitoring occupational exposure to chromium compounds. However, chromium(III) is an essential nutrient, and levels in biological fluids might be enough to mask low level exposures. One environmental epidemiology study suggested that residence near a ferrochromium plant did not pose a risk of cancer (Axelsson and Rylander 1980), but an environmental study (which included oral exposure due to contaminated well water) in China found that residence near an alloy plant that smelted chromium was associated with increased incidences of lung and stomach cancer (Zhang and Li 1987).

Mechanisms of Action. Numerous studies have investigated the mechanisms of cellular toxicity and genotoxicity. Toxicity appears to be related partly through reactive intermediates during intracellular reduction of chromium(VI) and oxidative reactions, and partly mediated by chromium(III), which is the final product of intracellular chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Shrivastava et al. 2002; Zhitkovich 2005). The products of metabolic reduction of chromium(VI) (free radicals and chromium(V) and (IV)) and the newly generated chromium(III) are thought to be, in part, primarily responsible for the genotoxic effects that lead to carcinogenicity seen in human and animal studies. The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al.

2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Results of other studies suggest that genotoxicity of chromium is due to the formation of chromium-DNA ternary adducts, which lead to repair errors, collapsed replication forks, alterations in cellular communication, and effects on signaling pathways and cytoskeleton (Ha et al. 2004), and centrosome and spindle assembly checkpoint bypass leading to chromosome instability (Holmes et al. 2006; Wise et al. 2006a). Studies on mechanisms of action of chromium are actively ongoing in the current and future literature (see Section 3.12.3, Ongoing Studies).

Biomarkers of Exposure and Effect.

Exposure. There are studies correlating chromium in urine (Gylseth et al. 1977; Iarmarcovai et al. 2005; Kilburn et al. 1990; Lindberg and Vesterberg 1983a; Lukanova et al. 1996; Medeiros et al. 2003a; McAughey et al. 1988; Minoia and Cavalleri 1988; Muttamara and Leong 2004; Mutti et al. 1985b; Sjogren et al. 1983; Stridsklev et al. 2004; Tola et al. 1977), blood (Iarmarcovai et al. 2005; Kilburn et al. 1990; Medeiros et al. 2003a; McAughey et al. 1988; Minoia and Cavalleri 1988; Muttamara and Leong 2004; Randall and Gibson 1987; Stridsklev et al. 2004; Sathwara et al. 2007), hair (Randall and Gibson 1989; Saner et al. 1984; Takagi et al. 1986), and erythrocytes (Lukanova et al. 1996; Minoia and Cavalleri 1988) to occupational exposure levels. All current methods of biological monitoring are useful primarily for occupational exposure scenarios. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989); the usefulness of this method for detecting prior exposures is limited to a timespan of months (Simpson and Gibson 1992). Erythrocytes (with a half-life of 120 days) can be used to monitor intermediate exposures, and blood or urine can be used to determine acute exposures (Korallus 1986a, 1986b). Occupational exposure to chromium can cause chromosomal aberrations (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Therefore, chromosomal abnormalities may be useful for monitoring chromium exposure; however, other chemicals are capable of causing these effects. Chromium(VI) compounds are able to bind to macromolecules in the body and can form DNA-protein crosslinks (Coogan et al. 1991b). However, no increase in these crosslinks was observed in leukocytes from volunteers over a 240-minute time period after ingestion of chromium(VI) as potassium chromate (Kuykendall et al. 1996). The identification of chromium-protein/peptide complexes specific for chromium(VI) exposure and small enough to be excreted in the urine may be useful for biomonitoring in detecting low level exposure to populations near hazardous waste sites. As discussed in Section 3.8.1,

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there are a number of limitations to using urinary monitoring to assess environmental exposure to chromium (Paustenbach et al. 1997). However, urinary monitoring has the advantage of easy sample collection and is noninvasive. Mathematical models have been used to identify “excess” urinary chromium in a population exposed to low levels of chromium (Fagliano et al. 1997). Further refinement of these models as more data are collected from unexposed and exposed populations will also be useful in detecting low level exposures.

Effect. Chromosomal aberrations have been observed in workers exposed by inhalation to chromium compounds (Koshi et al. 1984; Sarto et al. 1982; Stella et al. 1982). Moreover, chromium(VI) compounds can bind to macromolecules that are excreted in the urine (Coogan et al. 1991b). The use of these techniques to detect chromosomal aberrations and chromium-macromolecular complexes would be useful in identifying populations near hazardous waste sites that would be at higher risk. In addition, the finding of increased retinol binding protein, β_2 -microglobulin, and brush border proteins in the urine of workers exposed to chromium may serve as an early indication of kidney damage (Franchini and Mutti 1988; Lindberg and Vesterberg 1983b; Liu et al. 1998; Mutti et al. 1985b). Additional screening for low molecular weight proteins in occupationally exposed individuals will help to determine if these proteins can be used as reliable indicators of renal damage due to chromium exposure. Snyder et al. (1996) found no difference in mitogenic stimulation of mononuclear cells isolated from people environmentally/occupationally exposed to chromium as compared to nonexposed individuals. However, monocytes in the exposed population had a 36% lower level of the cytokine IL-6 that is involved in antibody production. As discussed in Section 3.3, chromium induces many types of DNA lesions such as chromium-DNA complexes, DNA adducts, and DNA-protein crosslinks that are potential markers of genotoxic or cancer effects due to chromium exposure. However, only one study has attempted to utilize such end points and reported that volunteers exposed to chromium in drinking water showed no increase in protein-DNA crosslinking in blood cells (Kuykendall et al. 1996). However, further studies may show that other types of lesions induced by chromium may be more sensitive. Räsänen et al. (1991) developed an *in vitro* method to assess chromium sensitivity by measuring mononuclear leukocyte proliferation in response to chromium(III) chloride, sodium chromate(VI), and potassium chromate(VI). Additional studies would be useful to validate this method.

Absorption, Distribution, Metabolism, and Excretion. The pharmacokinetics database is substantial for human and animal exposure to chromium compounds. Chromium and its compounds can be absorbed after oral (Anderson 1981, 1986; Anderson et al. 1983; Bunker et al. 1984; DiSilvestro and Dy 2007; Donaldson and Barreras 1966; Finley et al. 1996b; Gargas et al. 1994; Kerger et al. 1997;

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Kuykendall et al. 1996; Paustenbach et al. 1996), inhalation (Adachi et al. 1981; Cavalleri and Minoia 1985; Gylseth et al. 1977; Langård et al. 1978; Kiilunen et al. 1983; Mancuso 1997b; Minoia and Cavalleri 1988; Randall and Gibson 1987; Suzuki et al. 1984; Tossavainen et al. 1980), and dermal (Baranowska-Dutkiewicz 1981; Brieger 1920; Corbett et al. 1997; Liden and Lundberg 1979; Mali et al. 1963; Samitz and Shrager 1966; Spruit and van Neer 1966; Wahlberg 1970; Wahlberg and Skog 1965) exposure. For the general population, oral exposure via the diet to chromium(III) is the most significant route. Occupational exposure usually involves inhalation and dermal routes. Pharmacokinetic data are generally consistent with regard to absorption, distribution, and excretion among species. Chromium(VI) compounds are absorbed more readily through cell membranes than are chromium(III) compounds (MacKenzie et al. 1958; Maruyama 1982; Witmer et al. 1989, 1991). Absorption is greater through the lungs than through the gastrointestinal tract (Baetjer et al. 1959b; Bragt and van Dura 1983; Kuykendall et al. 1996; Visek et al. 1953; Wiegand et al. 1984, 1987).

Examination of tissues taken at autopsy from occupationally and environmentally exposed people indicate widespread distribution of chromium (Brune et al. 1980; Hyodo et al. 1980; Kollmeier et al. 1990; Mancuso 1997b; Schroeder et al. 1962; Teraoka 1981). Widespread distribution of chromium has also been found in animals after oral exposure (Kargacin et al. 1993; Witmer et al. 1989, 1991). The distribution of chromium in animals after intratracheal, parenteral, or dermal exposure is greatest in the lungs, liver, kidneys, blood, spleen, testes, and brain (Baetjer et al. 1959a; Behari and Tandon 1980; Bryson and Goodall 1983; Coogan et al. 1991b; Lim et al. 1983; Mutti et al. 1979; Tandon et al. 1979; Visek et al. 1953; Wahlberg and Skog 1965; Weber 1983). Oral exposure studies indicate that higher levels of chromium(VI) compounds are absorbed than are levels of chromium(III) compounds. Studies in humans occupationally and environmentally exposed to chromium(VI) (Casey and Hambidge 1984; Shmitova 1980) and in animals exposed to chromium(VI) or chromium(III) demonstrate the ability for chromium to cross the placenta (Mertz et al. 1969; Saxena et al. 1990a). Chromium(VI) crosses more readily than chromium(III).

There are no data to indicate that the route of exposure influences the metabolism of chromium. Regardless of the route of exposure, chromium(VI) inside the body is reduced to chromium(III) by ascorbic acid, glutathione, or by the NADPH-dependent cytochrome P450 system (Aaseth et al. 1982; Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; De Flora et al. 1984, 1997; Ding and Shi 2002; Garcia and Jennette 1981; Gruber and Jennette 1978; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; Liu et al. 1995; Mikalsen et al. 1989; O'Brien et al. 2003; Paustenbach et al. 2003; Petrilli et al.

1985, 1986a; Samitz 1970; Shrivastava et al. 2002; Suzuki and Fukuda 1990; Wiegand et al. 1984; Zhitkovich 2005).

Analysis of the urine of workers occupationally exposed to chromium(VI) indicates that chromium is excreted in the trivalent form, which is consistent with *in vivo* reduction of chromium(VI) to chromium(III) (Cavalleri and Minoia 1985; Minoia and Cavalleri 1988). Oral studies in humans and animals indicate that most of the chromium(VI) or chromium(III) ingested is excreted in the feces (Bunker et al. 1984; Donaldson and Barreras 1966; Donaldson et al. 1984; Henderson et al. 1979; Sayato et al. 1980), consistent with the poor gastrointestinal absorption of chromium. After dermal exposure of humans and animals, chromium can be found in the urine and feces (Brieger 1920; Wahlberg and Skog 1965). Chromium has been detected in hair and fingernails of the general population of several countries (Takagi et al. 1986, 1988) and in the breast milk of nursing mothers (Casey and Hambidge 1984), indicating these media as routes of excretion. Data regarding excretion after exposure of animals to chromium(VI) or chromium(III) by other routes indicated that excretion occurs rapidly, and primarily via the kidneys, once chromium(VI) is reduced (Gregus and Klaassen 1986; Yamaguchi et al. 1983). Thus, absorption, distribution, and excretion of chromium have been studied extensively. Additional studies examining the enzymatic reduction of chromium(VI) compounds in rodents and humans would be of value in determining the potential biological impact of the reported differences in those pathways.

Comparative Toxicokinetics. Toxicokinetic data in humans, dogs, rats, mice, rabbits, and hamsters generally correlate well among species (see references above). However, exposures to chromium(VI) resulted in different organ distribution patterns between rats and mice (Kargacin et al. 1993), and the chromium levels in mouse fetal tissues were elevated over maternal blood levels, whereas in rats, these differences were not found (Saxena et al. 1990a). In addition, comparisons of human and rat hepatic microsomal ability to reduce chromium(VI) indicated differences in microsomal complexes involved (Myers and Myers 1998; Pratt and Myers 1993). Therefore, additional comparison studies among species would be useful to determine variations in the absorption, distribution, metabolism, and excretion of chromium. A PBPK model (O'Flaherty 1996; O'Flaherty et al. 2001) that has been partially validated has been developed based on rats. As described previously, the model is quite sophisticated, but additional physiological and kinetic parameters from both humans and other animal species are needed in order for the model to be employed for extrapolation across species and for use in risk assessment. Furthermore, additional metabolic data are needed with regard to insoluble chromium and its elimination and solubilization, particularly in lung tissue.

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Methods for Reducing Toxic Effects. Methods for reducing the absorption of chromium from the lungs consist primarily of administering ascorbic acid or N-acetylcysteine, which enhance the reduction of chromium(VI) to chromium(III) (De Flora and Wetterhahn 1989; Suzuki and Fukuda 1990). Chromium(III) passes the alveolar lining into the bloodstream less readily than chromium(VI) and is cleared by mucociliary clearance. A study might be conducted to determine whether administration of expectorants would enhance clearance from the lungs. Oral administration of ascorbic acid to further reduce chromium(VI) to chromium(III) might further decrease bioavailability (Haddad et al. 1998; Kuykendall et al. 1996; Schonwald 2004), although this has not been proven (Leikin and Paloucek 2002; Schonwald 2004). After dermal exposure, thorough washing and ascorbic acid therapy to enhance the reduction of chromium(VI) to chromium(III) (Schonwald 2004), followed by chelation with EDTA (Nadig 1994), would greatly reduce dermal absorption. Administration of ascorbic acid has also been used to enhance the reduction of chromium(VI) to chromium(III) in plasma (Korallus et al. 1984), which would reduce the body burden of chromium because chromium(III) would bind to plasma protein and be excreted in the urine. Studies could be conducted to determine if other reducing agents would be more effective than ascorbic acid. Once inside the cell, chromium(VI) can enter many reactions resulting in reduction to various oxidation states with the generation of reactive oxygen species and radicals, all of which may be more or less toxic than chromium(III) (De Flora and Wetterhahn 1989). Gasiorowski et al. (1997, 1998) showed that stabilizing chromium in the hexavalent oxidation state, via complexing to a ligand, decreased the mutagenicity of chromium(VI). Methods could be developed to interfere with these various reactions, but such methods may be counterproductive because they might shift one reaction to another with undesirable consequences. *In vitro* studies have indicated that vitamin E, ascorbic acid, and glutathione protected against cellular damage, including chromosomal breakage, DNA-protein crosslinks, and apoptosis (cell death) (Blankenship et al. 1997; Little et al. 1996; Sugiyama 1991; Wise et al. 1993, 2004), while vitamin B₂ enhanced the cytotoxicity and DNA single-strand breaks induced by chromium(VI) (Sugiyama 1991). Vitamin E may have scavenged radicals and/or chromium(V) during the reduction of chromium(VI) (Sugiyama 1991). Other vitamins might also be effective in mitigating chromium's effects; thus, studies on the effect of vitamins on chromium toxicity may provide additional information on the potential to reduce toxic effects. Although the administration of thyroxine has been shown to ameliorate potassium dichromate-induced acute renal failure in rats (Siegel et al. 1984), its use in humans has not been tested. Further studies are needed to assess the safety of administering thyroxine to mitigate chromium toxicity.

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Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

A limited amount of information is available on the toxicity of chromium in children; most of the available data come from children ingesting lethal doses of chromium(VI) (Clochesy 1984; Ellis et al. 1982; Iserson et al. 1983; Kaufman et al. 1970; Reichelderfer 1968). Studies that examine sensitive end points such as respiratory effects following inhalation exposure, or gastrointestinal, hematological, liver and kidney effects in young animals would be useful for assessing whether children will be unusually susceptible to chromium toxicity. The available animal data suggest that chromium is a developmental toxicant. As discussed in Section 3.2.2.6, the observed developmental effects include postimplantation losses, gross abnormalities, and impaired reproductive development in the offspring (Al-Hamood et al. 1998; Junaid et al. 1996a, 1996b; Kanojia et al. 1996, 1998; Trivedi et al. 1989). Data needs relating to development are discussed in detail in the Developmental Toxicity subsection above. There are some data in humans and animals that provide evidence that chromium can cross the placenta and be transferred to an infant via breast milk (Casey and Hambidge 1984; Danielsson et al. 1982; Mertz et al. 1969; Saxena et al. 1990a; Shmitova 1980). There are no data on whether chromium is stored in maternal tissues and whether these stores can be mobilized during pregnancy or lactation.

An age-related difference in the extent of gastrointestinal absorption of chromium(III) was reported in one study (Sullivan et al. 1984); it is not known if a similar relationship would exist for chromium(VI). No other information is available that evaluated potential differences between adults and children.

Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of chromium, particularly chromium(VI) would be useful in assessing children's susceptibility to chromium toxicity. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. There is very little available information on methods for reducing chromium toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to chromium toxicity have been identified and are shown in [Table 3-12](#).

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Table 3-12. Ongoing Studies on Chromium

Investigator	Study Topic	Institution	Sponsor
Avery S	Role of oxidative mechanisms in the toxicity of metals	University of Nottingham	National Institute of General Medical Sciences
Cohen M	Properties of metals may govern toxicities in the lungs	New York University School of Medicine	National Institute of General Medical Sciences
Myers C	Human lung chromium toxicity: Role of cytochrome b5	Medical College of Wisconsin	National Institute of Environmental Health Sciences
Patierno S	Chromium genotoxicity: Response and repair mechanisms	George Washington University	National Institute of Environmental Health Sciences
Stearns D	Uptake and mutagenicity of moderately soluble hexavalent chromium	Northern Arizona University	National Institute of Environmental Health Sciences
Sugden K	Oxidative DNA lesion formation from chromate exposure	University of Montana	National Institute of Environmental Health Sciences
Zhitkovich A	Biological dosimetry of hexavalent chromium	Brown University	National Institute of Environmental Health Sciences
Zhitkovich A	Genotoxicity of chromium compounds	Brown University	National Institute of Environmental Health Sciences
Zhitkovich A	Sensitivity mechanisms in chromium toxicity	Brown University	National Institute of Environmental Health Sciences

Source: FEDRIP 2008

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chromium is located in [Table 4-1](#).

The synonyms, trade name, chemical formula, and identification numbers of chromium and selected salts are reported in [Table 4-1](#).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

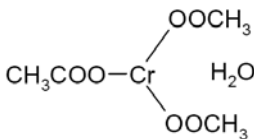
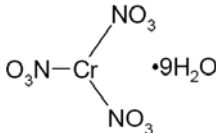
Information regarding the physical and chemical properties of chromium is located in [Table 4-2](#).

Chromium is a metallic element with oxidation states ranging from chromium(-II) to chromium(+VI) with the trivalent (III) and hexavalent (VI) states being the most predominant. The Chemical Abstracts Service (CAS) Registry numbers for trivalent and hexavalent chromium are 16065-83-3 and 18540-29-9, respectively. Elemental chromium, chromium(0), does not occur naturally. Although there is a divalent state, chromium II (chromous), it is relatively unstable under environmental conditions and is readily oxidized to the trivalent (III or chromic) state. Chromium compounds are most stable in the trivalent state under environmental conditions and occur in nature in ores, such as ferrochromite (FeCr_2O_4). The hexavalent (VI or chromate) is the second most stable state; however, it only occurs naturally in rare minerals such as crocoite (PbCrO_4) (Hurlbut 1971; Papp and Lipin 2001). Hexavalent chromium compounds primarily arise from anthropogenic sources (Alimonti et al. 2000; Barceloux 1999; EPA 1984a; Johnson et al. 2006; Shanker et al. 2005).

The solubility of chromium compounds varies, depending primarily on the oxidation state. Trivalent chromium compounds, with the exception of acetate, hexahydrate of chloride, and nitrate salts, are generally insoluble in water ([Table 4-2](#)). The zinc and lead salts of chromic acid are practically insoluble in cold water ([Table 4-2](#)). The alkaline metal salts (e.g., calcium, strontium) of chromic acid are slightly soluble in water. Some hexavalent compounds, such as chromium(VI) oxide (or chromic acid), and the ammonium and alkali metal salts (e.g., sodium and potassium) of chromic acid are readily soluble in water. The hexavalent chromium compounds are reduced to the trivalent form in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, hexavalent chromium compounds are more stable (EPA 1984a; Loyaux-Lawniczak et al. 2001).

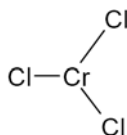
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Chromium(0)	Chromium(III) acetate, monohydrate	Chromium(III) nitrate, nonahydrate
Synonym(s)	Chrome; Chrom (German); Chrome (French)	Acetic acid, chromium salt, hydrate; chromic acetate, hydrate	Nitric acid, chromium (III) salt, nonahydrate; chromium nitrate, nonahydrate
Registered trade name(s)	Chrome	No data	No data
Chemical formula	Cr	$\text{Cr}(\text{CH}_3\text{COO})_3 \cdot \text{H}_2\text{O}$	$\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$
Chemical structure	Cr		
Identification numbers:			
CAS registry	7440-47-3	25013-82-5	7789-02-8
NIOSH RTECS	GB420000	AG3053333	GB6300000
EPA hazardous waste	D007	No data	No data
OHM/TADS	7216647	No data	No data
DOT/UN/NA/IMDG shipping	Not assigned	No data	No data
HSDB	910	No data	No data
NCI	Not assigned	No data	No data

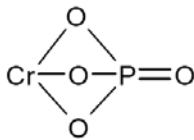
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Chromium(III) chloride	Chromium(III) chloride, hexahydrate	Chromite (Cr ₂ FeO ₄) (Chromium[III])
Synonym(s)	Chromium trichloride	Hexaaquachromium (III) chloride	Chromite; chromite ore; chromite homog mineral; chromite (mineral)
Registered trade name(s)	C177295	No data	No data
Chemical formula	CrCl ₃	Cr(Cl) ₃ •6H ₂ O	FeCr ₂ O ₄
Chemical structure	<div>Cr[Cl₂(H₂O)₄]Cl•2H₂O</div> <div>FeOCr₂O₃</div> <div></div>		
Identification numbers:			
CAS registry	10025-73-7	10060-12-5	1308-31-2
NIOSH RTECS	GB5425000	GB5450000	GB4000000
EPA hazardous waste	No data	No data	D007
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	No data	2963
NCI	No data	No data	No data

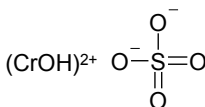
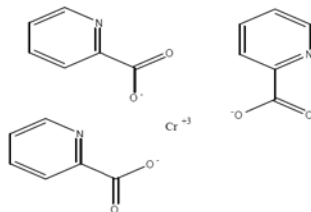
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Chromium(III) oxide	Chromium(III) phosphate	Chromium(III) sulfate
Synonym(s)	Chromium sesquioxide; dichromium trioxide; chromic oxide	Chromumorthophosphate; phosphoric acid, chromium (III) salt	Sulfuric acid, chromium (III) salt
Registered trade name(s)	No data	Amaudon's Green	Chromitan B
Chemical formula	Cr_2O_3	CrPO_4	$\text{Cr}_2(\text{SO}_4)_3$
Chemical structure	$\text{O}=\text{Cr}-\text{O}-\text{Cr}=\text{O}$		$\text{SO}_4=\text{Cr}-\text{SO}_4-\text{Cr}=\text{SO}_4$
Identification numbers:			
CAS registry	1308-38-9	7789-04-0	10101-53-8
NIOSH RTECS	GB6475000	GB6840000	GB7200000
EPA hazardous waste	D007	No data	D0007
OHM/TADS	Not assigned	No data	7800052
DOT/UN/NA/IMDG shipping	Not assigned	No data	Not assigned
HSDB	1619	No data	2543
NCI	Not assigned	No data	Not assigned

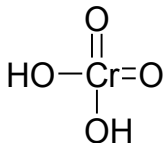

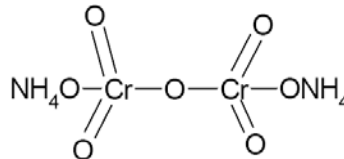
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Sodium chromite (Chromium[III])	Chromium hydroxide sulfate (Chromium III)	Chromium(III) picolinate
Synonym(s)	No data	Chromium hydroxide sulfate (Cr(OH)(SO ₄)); basic chromium sulfate	CrPic; Chromium 2-pyridinecarboxylate; Chromium tris(picolinato)-; Picolinic acid, chromium salt
Registered trade name(s)	No data	No data	No data
Chemical formula	NaCrO ₂	CrOH ₂ SO ₄	C ₁₈ H ₁₂ CrN ₃ O ₆
Chemical structure	NaO-Cr=O		
Identification numbers:			
CAS registry	12314-42-0	12336-95-7	14639-25-9
NIOSH RTECS	No data	GB6240000	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	No data	No data
NCI	No data	No data	No data

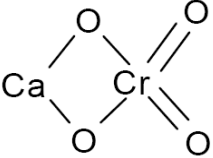
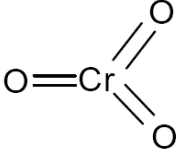
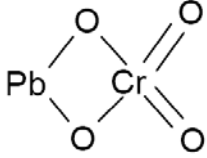
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Chromic acid (Chromium VI)	Chromium(IV) oxide	Ammonium dichromate (Chromium[VI])
Synonym(s)	Acide chromique; chromic(VI) acid	Chromium dioxide	Chromic acid, diamonium salt
Registered trade name(s)	No data	No data	No data
Chemical formula	H ₂ CrO ₄	CrO ₂	(NH ₄) ₂ Cr ₂ O ₇
Chemical structure			
Identification numbers:			
CAS registry	7738-94-5	12018-01-8	7789-09-5
NIOSH RTECS	GB6650000	GB6400000	HX7650000
EPA hazardous waste	No data	D007	Not assigned
OHM/TADS	No data	No data	7217321
DOT/UN/NA/IMDG shipping	1755	No data	UN1439; IM05.1
HSDB	6769	1620	481
NCI	No data	No data	No data

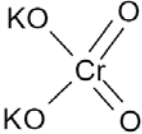
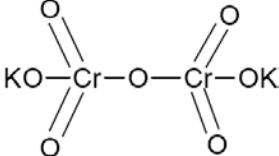
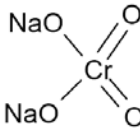
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Calcium chromate (Chromium[VI])	Chromium(VI) trioxide	Lead chromate (Chromium[VI])
Synonym(s)	Chromic acid, calcium salt	Chromic acid, chromium anhydride	Chromic acid, lead salt
Registered trade name(s)	Calcium Chrome Yellow	No data	Chrome Yellow G
Chemical formula	CaCrO ₄	CrO ₃	PbCrO ₄
Chemical structure			
Identification numbers:			
CAS registry	13765-19-0	1333-82-0	7758-97-6
NIOSH RTECS	GB2750000	GB6650000	GB2975000
EPA hazardous waste	U032; D007	D007	D007; D008
OHM/TADS	7800051	Not assigned	Not assigned
DOT/UN/NA/IMDG shipping	NA9096	YB1463/UN15.1; IM05.1	Not assigned
HSDB	248	518; NA1463	1650
NCI	Not assigned	UN1463	Not assigned

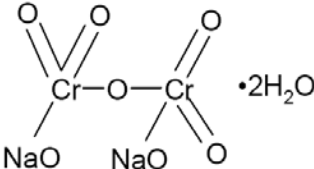
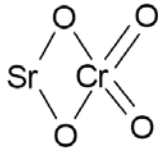
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information		
Chemical name	Potassium chromate (Chromium[VI])	Potassium dichromate (Chromium[VI])	Sodium chromate (Chromium[VI])
Synonym(s)	Chromic acid, dipotassium salt	Chromic acid, dipotassium salt	Chromic acid, disodium salt
Registered trade name(s)	No data	No data	Caswell No. 757
Chemical formula	K ₂ CrO ₄	K ₂ Cr ₂ O ₇	Na ₂ CrO ₄
Chemical structure			
Identification numbers:			
CAS registry	7789-00-6	7778-50-9	7775-11-3
NIOSH RTECS	GB2940000	HX7680000	GB2955000
EPA hazardous waste	No data	No data	D007
OHM/TADS	7217277	7217278	7216891
DOT/UN/NA/IMDG shipping	NA9142	NA1479; IM09.0	No data
HSDB	1249	1238	2962
NCI	Not assigned	Not assigned	Not assigned

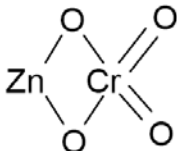
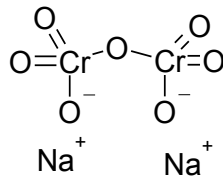
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information	
Chemical name	Sodium dichromate, dihydrate (Chromium[VI])	Strontium chromate (Chromium[VI])
Synonym(s)	Chromic acid, disodium salt; dihydrate	Chromic acid, strontium salt
Registered trade name(s)	No data	No data
Chemical formula	$\text{NaCr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$	SrCrO_4
Chemical structure		
Identification numbers:		
CAS registry	7789-12-0	7789-06-2
NIOSH RTECS	HX7750000	GB3240000
EPA hazardous waste	No data	D007
OHM/TADS	No data	780058
DOT/UN/NA/IMDG shipping	No data	NA9149
HSDB	No data	2546
NCI	No data	Not assigned

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Chromium and Compounds

Characteristic	Information	
Chemical name	Zinc chromate (Chromium[VI])	Sodium dichromate (Chromium VI)
Synonym(s)	Chromic acid, zinc salt	Chromic acid (H ₂ Cr ₂ O ₇), sodium salt (1:2)
Registered trade name(s)	CI Pigment Yellow	No data
Chemical formula	ZnCrO ₄	Na ₂ Cr ₂ O ₇
Chemical structure		
Identification numbers:		
CAS registry	13530-65-9	10588-01-9
NIOSH RTECS	GB3290000	HX7700000
EPA hazardous waste	D007	D007
OHM/TADS	7217401	No data
DOT/UN/NA/IMDG shipping	Not assigned	3288
HSDB	6188	737
NCI	Not assigned	No data

Sources: HSDB 2012; NIOSH 2005

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromium	Chromium(III) acetate, monohydrate	Chromium(III) nitrate, nonahydrate	Chromium(III) chloride
Molecular weight	51.996	229.13	400.15	158.35
Color	Steel-gray	Gray-green or bluish-green	Purple or violet	Violet or purple
Physical state	Solid	Solid	Solid	Solid
Melting point	1,90±10 °C	No data	60 °C	≈1,150 °C
Boiling point	2,642 °C	No data	Decomposes at 100 °C	Decomposes at 1,300 °C
Density at 20 °C	7.14 (28 °C) ^a	No data	No data	2.87 (25 °C) ^a
Odor	odorless	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	Insoluble	Soluble	Soluble	Slightly soluble in hot water
Organic solvents	Insoluble in common organic solvents	45.4 g/L in methanol (15 °C); 2 g/L in acetone (15 °C)	Soluble in ethanol and acetone	Insoluble in cold water, acetone, methanol, and ether
Partition coefficients:				
Log K _{ow}	Not applicable	Not applicable	Not applicable	Not applicable
Log K _{oc}	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	1 mmHg (1,616 °C)	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromium(III) chloride, hexahydrate	Ferrochromite (Chromium[III])	Chromium(III) oxide	Chromium(III) phosphate
Molecular weight	266.45	223.84	151.99	146.97
Color	Violet	Brown-black	Green	Gray-brown to black ^d
Physical state	Solid	Solid	Solid	Solid
Melting point	83 °C	No data	2,435 °C	>1,800 °C
Boiling point	No data	No data	3,000 °C	No data
Density at 20 °C	1.76 ^b	4.97 (20 °C)	5.22 (25 °C) ^b	2.94 (32.5 °C) ^{a,c}
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	58.5 g/100 cc at 25 °C	Insoluble	Insoluble	Insoluble ^c
Organic solvents	Soluble in ethanol	No data	Insoluble in ethanol	Insoluble in alcohol, acetone
Partition coefficients:				
Log K _{ow}	No data	Not applicable	Not applicable	Not applicable
Log K _{oc}	No data	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	No data
Henry's law constant at 25 °C	No data	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromium(III) sulfate	Sodium chromite (Chromium[III])	Chromium hydroxide sulfate (Chromium III) ^e	Chromium(III) picolinate
Molecular weight	392.18	106.98	165.1	418.3 ^c
Color	Violet, red, peach	No data	Green powder	Ruby red ^d
Physical state	Solid	No data	Solid	Crystal ^d
Melting point	No data	No data	>900 °C	No data
Boiling point	No data	No data	No data	No data
Density at 20 °C	3.012	No data	1.25	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	Insoluble	No data	2,000 g/L	1 ppm at 25 °C ^d
Organic solvents	soluble in alcohols	No data	No data	>6 g/L (DMSO) ^d
Partition coefficients:				
Log K _{ow}	Not applicable	Not applicable	Not applicable	1.753 ^f
Log K _{oc}	Not applicable	Not applicable	Not applicable	No data
Vapor pressure at 20 °C	No data	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Chromic acid (Chromium[VI])	Chromium(IV) oxide	Ammonium dichromate (Chromium[VI])
Molecular weight	118	83.99	252.07
Color	Dark purple-red	Brown-black	Orange
Physical state	Solid	Solid	Solid
Melting point	196 °C	Decomposes at 300 °C	Decomposes at 180 °C
Boiling point	Decompose before boiling	Not applicable	Not applicable
Density at 20 °C	1.67–2.82	No data	2.15 (25 °C) ^a
Odor	No data	No data	odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	1x10 ⁶ mg/L at 17 °C	Insoluble	In water (wt/wt): 15.5% (0 °C); 26.67% (20 °C); 36.99% (40 °C); 46.14% (60 °C); 54.20% (80 °C)
Organic solvents	Soluble in alcohol and mineral acids	No data	Soluble in alcohols, insoluble in acetone
Partition coefficients:			
Log K _{ow}	Not applicable	Not applicable	Not applicable
Log K _{oc}	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Calcium chromate (Chromium[VI])	Chromium(VI) trioxide	Lead chromate (Chromium[VI])	Potassium chromate (Chromium[VI])
Molecular weight	156.07	99.99	323.19	194.19
Color	Yellow	Red	Yellow	Yellow
Physical state	Solid	Solid	Solid	Solid
Melting point	No data	197 °C	844 °C	975 °C
Boiling point	No data	Decomposes	Decomposes	No data
Density at 20 °C	2.89 ^b	2.70 (25 °C)	6.12 (15 °C)	2.732 (18 °C)
Odor	No data	Odorless	No data	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20 °C	2.23 g/100 mL	61.7 g/100 cc at 0 °C	5.8 µg/100 mL	62.9 g/100 at 20 °C
Organic solvents	No data	Soluble in ethanol, ethyl ether, sulfuric and nitric acids	Soluble 0.2 mg/l water	62.9 G/100 cc water (20 °C)
		Soluble 61.7 g/100 cc water (0 °C)	Insoluble in acetic acid; soluble in dilute nitric acid and in solution of fixed alkali hydroxides	79.2 g/100 cc water (100 °C)
		67.45 g/100 cc water (100 °C)	Soluble in acid, insoluble in ammonia	Insoluble in alcohol
		167.299 lb/100 lb water (70 °F)		
		Soluble in acetic acid and acetone		
Partition coefficients:				
Log K _{ow}	Not applicable	Not applicable	Not applicable	Not applicable
Log K _{oc}	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data	0
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Potassium dichromate (Chromium[VI])	Sodium chromate (Chromium[VI])	Sodium dichromate, dihydrate (Chromium[VI])
Molecular weight	294.18	161.97	298.00
Color	Red	Yellow	Red
Physical state	Solid	Solid	Solid
Melting point	398 °C	792 °C	356.7 °C
Boiling point	Decomposes at 500 °C	No data	Decomposes at 400 °C
Density at 20 °C	2.676 (25 °C)	2.710–2.736 ^b	2.52 (13 °C)
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	4.9 g/100 cc at 0 °C	87.3 g/100 cc at 30 °C	230 g/100 cc at 0 °C
Organic solvents	Insoluble in ethanol and acetone	Soluble in methanol	Insoluble in ethanol
Partition coefficients:			
Log K _{ow}	Not applicable	Not applicable	Not applicable
Log K _{oc}	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Chromium and Compounds

Property	Strontium chromate (Chromium[VI])	Zinc chromate (Chromium[VI])	Sodium dichromate (Chromium[VI])
Molecular weight	203.61	181.97	262
Color	Yellow	Lemon-yellow	Bright orange-red
Physical state	Solid	Solid	Solid
Melting point	No data	No data	356.7 °C
Boiling point	No data	No data	Decomposes at 400 °C
Density at 20 °C	3.895 (15 °C)	3.40 ^b	2.52 at 13 °C
Odor	No data	Odorless	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 20 °C	0.12 g/100 cc at 15 °C	Insoluble	2,380 g/L at 0 °C
Organic solvents	Soluble in acetyl acetone	Insoluble in acetone	513.4 g/L (methanol)
Partition coefficients:			
Log K _{ow}	Not applicable	Not applicable	Not applicable
Log K _{oc}	Not applicable	Not applicable	Not applicable
Vapor pressure at 20 °C	No data	No data	No data
Henry's law constant at 25 °C	Not applicable	Not applicable	Not applicable
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

^aTemperature at which the densities were measured has been given only when such data are available^bTemperature at which density was measured was not specified.^cO'Neil et al. 2006^dBroadhurst et al. 1997^eIPCS 2004^fChakov et al. 1999

DMSO=dimethylsulfoxide

4. CHEMICAL AND PHYSICAL INFORMATION

In humans, chromium(III) is an essential nutrient that may play a role in glucose, fat, and protein metabolism possibly by potentiating the action of insulin. However, there is some emerging controversy whether chromium(III) is essential and more work has been suggested to elucidate its mechanism of action. Chromium picolinate, a trivalent form of chromium complexed with picolinic acid, is used as a dietary supplement, because it is claimed to speed metabolism and may have anti-diabetic effects (Broadhurst et al. 1997). However, there still remains controversy over the use of chromium(III) in diabetes, and several researchers claim no demonstrated effects of chromium(III) on diabetes or insulin resistance (Althuis et al. 2002). Currently, the mechanism of transport and absorption of chromium picolinate has not been determined, although spectroscopic analysis has shown that chromium picolinate is a very stable complex in the body and its absorption properties may be due to its ability to cross membranes (Chakov et al. 1999).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Tables 5-1 and 5-2 list the facilities in each state that manufacture or process chromium, the intended use, and the range of maximum amounts of chromium that are stored on site. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI) (TRI09 2011). The data presented in Table 5-1 are for chromium metal and the data from Table 5-2 are for all chromium compounds. Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Chromium metal is commercially produced in the United States by the reduction of chromite ore with carbon, aluminum, or silicon, and subsequent purification. Sodium chromate and dichromate are produced by roasting chromite ore with soda ash. Most other chromium compounds are produced from sodium chromate and dichromate (Hartford 1979; Papp and Lipin 2001; Westbrook 1979). For example, basic chromic sulfate ($\text{Cr}(\text{OH})\text{SO}_4$), commonly used in tanning, is commercially produced by the reduction of sodium dichromate with organic compounds (e.g., molasses) in the presence of sulfuric acid or by the reduction of dichromate with sulfur dioxide. Lead chromate, commonly used as a pigment, is produced by the reaction of sodium chromate with lead nitrate or by reaction of lead monoxide with chromic acid solution (IARC 1990).

The major manufacturers of chromium compounds in 2007 are summarized in Table 5-3 (SRI 2007).

Tables 5-1 and 5-2 report the number of facilities in each state that manufacture and process chromium, the intended use of the products, and the range of maximum amounts of chromium products that are stored on site. The data reported in Tables 5-1 and 5-2 are derived from TRI of EPA (TRI09 2011). The TRI data should be used with caution since only certain types of facilities were required to report. Hence, this is not an exhaustive list.

5.2 IMPORT/EXPORT

Chromite ore and foundry sand; chromium chemicals, ferroalloys, and metal; and stainless steel represent the bulk of the market for chromium. In 2006, the United States produced chromium ferroalloys, metal, chemicals, and stainless steel. The United States is a major producer of the end products of chromium, which include chromium chemicals, metal, and stainless steel, but until recently, the United States had not mined chromium (Stokinger 1981; USGS 2008b). Oregon Resources Corporation (ORC), a subsidiary of

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Metallic Chromium

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	2	10,000	999,999	12
AL	106	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	63	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	68	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	190	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	60	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CT	83	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	12	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
FL	55	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
GA	103	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	2	0	99,999	1, 5, 8, 9
IA	96	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
ID	16	0	999,999	1, 3, 5, 8, 9, 10, 12, 13
IL	148	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	176	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	60	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	118	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	77	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	75	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	54	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	23	0	9,999,999	1, 2, 3, 5, 8, 9, 11, 12
MI	177	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	83	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	77	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	40	0	499,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 14
MT	14	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14
NC	94	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	14	1,000	999,999	1, 2, 3, 5, 7, 8, 9, 12, 13
NE	41	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NH	28	0	49,999,999	2, 3, 4, 6, 7, 8, 9, 11, 12
NJ	101	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	22	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
NV	48	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	130	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	251	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	91	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Metallic Chromium

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
OR	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	264	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	15	0	99,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12
RI	22	0	999,999	1, 2, 3, 6, 7, 8, 9, 11, 12
SC	108	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	18	100	999,999	1, 5, 7, 8, 9, 11, 12, 13, 14
TN	109	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	214	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	60	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	66	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	16	100	999,999	2, 3, 4, 6, 8, 9, 11
WA	75	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	134	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	51	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
WY	10	0	999,999	1, 8, 9, 11, 12, 13

^aPost office state abbreviations used.^bAmounts on site reported by facilities in each state.^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI09 2011 (Data are from 2009)

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Chromium Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	22	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AL	140	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	87	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	102	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	198	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	38	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CT	62	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	32	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
FL	91	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	128	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	10	1,000	999,999	1, 5, 6, 7, 8, 9, 12, 13, 14
IA	70	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	25	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IL	241	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	212	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	70	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	121	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	88	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	71	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	83	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	34	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MI	216	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	80	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	98	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	80	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
NC	134	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	17	1,000	999,999	1, 2, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
NE	44	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	17	0	99,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
NJ	129	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	38	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NV	47	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	154	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	330	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	75	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Chromium Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
OR	63	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	293	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	27	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
RI	23	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
SC	115	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	17	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
TN	142	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	319	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	76	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	78	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VT	9	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11
WA	86	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	141	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	85	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	25	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

^aPost office state abbreviations used.^bAmounts on site reported by facilities in each state.^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI09 2011 (Data are from 2009)

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-3. Major Manufacturers of Chromium Compounds in 2007

Chemical	Manufacturer	Location
Chromic anhydride	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromic hydrate	Elementis Chromium LP	Corpus Christi, Texas
Chromic sulfate	Blue Grass Chemical Specialties, LLC Elementis LTP L.P.	New Albany, Indiana Amarillo, Texas Dakota City, Nebraska Milwaukee, Wisconsin
Chromium(III) acetate	Johnson Matthey, Inc.; Alfa Aesar Blue Grass Chemical Specialties, LLC McGean-Rohco, Inc.; McGean Speciality Chemical Division The Shepherd Chemical Company	Ward Hill, Massachusetts New Albany, Indiana Cleveland, Ohio Cincinnati, Ohio
Chromium(III) acetylacetonate	MacKenzie Company The Shepherd Chemical Company	Bush, Louisiana Cincinnati, Ohio
Chromium boride	CERAC, Inc. Johnson Matthey, Inc.; Alfa Aesar	Milwaukee, Wisconsin Ward Hill, Massachusetts
Chromium carbonyl	Strem Chemicals Incorporated McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Newburyport, Massachusetts Cleveland, Ohio
Chromium(III) chloride	Blue Grass Chemical Specialties, LLC McGean-Rohco, Inc.; McGean Specialty Chemicals Division	New Albany, Indiana Cleveland, Ohio
Chromium diboride	Johnson Matthey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
Chromium difluoride	Atotech USA, Inc.	Rock Hill, South Carolina
Chromium 2-ethylhexanoate	OM Group, Inc. The Shepherd Chemical Company	Franklin, Pennsylvania Cincinnati, Ohio
Chromium fluoride	Atotech USA	Rock Hill, South Carolina
Chromium hexacarbonyl	Strem Chemicals Incorporated	Newburyport, Massachusetts
Chromium hydroxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium(III) hydroxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium hydroxyl diacetate	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium hydroxyl dichloride	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium naphthenate	OM Group, Inc.	Franklin, Pennsylvania
Chromium nitrate	Blue Grass Chemical Specialties, LLC McGean-Rohco Inc.; McGean Specialty Chemicals Division The Shepherd Chemical Company	New Albany, Indiana Cleveland, Ohio Cincinnati, Ohio
Chromium ocetenoate	OM Group, Inc. The Shepherd Chemical Company	Franklin, Pennsylvania Cincinnati, Ohio
Chromium octoate	OM Group, Inc. The Shepherd Chemical Company	Franklin, Pennsylvania Cincinnati, Ohio

Table 5-3. Major Manufacturers of Chromium Compounds in 2007

Chemical	Manufacturer	Location
Chromium oxide	Elementis Chromium LP	Corpus Christi, Texas
Chromium potassium sulfate	McGean-Rohco, Inc.; McGean Specialty Chemicals Division	Cleveland, Ohio
Chromium-silicon monoxide	CERAC, Inc.	Milwaukee, Wisconsin
Chromium(III) sulfate	Blue Grass Chemical Specialties, LLC Elementis LTP L.P.	New Albany, Indiana
		Amarillo, Texas
		Dakota City, Nebraska
		Milwaukee, Wisconsin
Chromotropic acid, disodium salt	Johnson Mathey, Inc.; Alfa Aesar Johnson-Mathhey, Inc.; Alfa Aesar	Ward Hill, Massachusetts
		Ward Hill, Massachusetts

Source: SRI 2007

Industrial Minerals Corporation (Australia), extracted bulk samples of chromite ore at its surface mine in Coos County, Oregon. ORC developed its material beneficiation process to recover chromite, garnet, and zircon minerals with production expected to start in 2008 (IMC 2007). Although chromium is currently mined in Oregon, the United States receives the majority of chromium ores from other countries. From 2003 to 2006, chromium contained in chromite ore and chromium ferroalloys and metal were imported from South Africa (34%), Kazakhstan (18%), Russia (7%), Zimbabwe (6%), and other (35%) (USGS 2008b).

U.S. imports and exports are summarized in [Table 5-4](#) (USGS 2008a).

5.3 USE

The metallurgical, refractory, and chemical industries are the fundamental users of chromium. In the metallurgical industry, chromium is used to produce stainless steels, alloy cast irons, nonferrous alloys, and other miscellaneous materials. In 1988, the U.S. chemical and metallurgical industries accounted for 83.9% and the refractory industry for 16.1% of the total domestic consumption of chromite (USDI 1988a). The stainless steel industry is the leading consumer of chromium materials. A significant amount of chromium is imported and exported in stainless steel mill products and scrap, with ferrochromiums as the main components used by the metallurgical industry. Typical weight percent of chromium in stainless steel and chromium alloys ranges from 11.5 to 30%. In the refractory industry, chromium is a component in chrome and chrome-magnesite, magnesite-chrome bricks, and granular chrome-bearing and granular chromite, which are used as linings for high temperature industrial furnaces. In the chemical industry, both chromium(III) and chromium(VI) are used primarily in pigments. Other uses include chromium(VI) in metal finishing, chromium(III) in leather tanning, and chromium(VI) in wood preservatives. [Table 5-5](#) lists the approximate distribution of use for chromium chemicals in the major applications in the United States and Western world in 1996 with a comparison to use in the United States for 1951 (Barnhart 1997). Smaller amounts of chromium are used as catalysts and in miscellaneous applications, such as drilling muds, chemical manufacturing, textiles, toners for copying machines, magnetic tapes, and dietary supplements (Carlton 2003; CMR 1988a, 1988b; Davis and Vincent 1997; EPA 1984a; IARC 1990; Papp and Lipin 2001; Radivojevic and Cooper 2008; USDI 1988a). Chromium alloys are also used in metal joint prostheses (Sunderman et al. 1989). Chromium picolinate, a trivalent form of chromium complexed with picolinic acid, is used as a dietary supplement, with the claim that it reduces symptoms of type II diabetes and hypoglycemia (Broadhurst et al. 1997), although a recent meta-review concludes that the results are still inconclusive (Althuis et al. 2002).

Table 5-4. U.S. Chromium Imports and Exports

Year	Imports (thousands of metric tons gross weight)	Exports (in thousands of metric tons gross weight)
2003	441	188
2004	489	171
2005	503	220
2006	520	212
2007	510	210

Source: USGS 2008a

Table 5-5. Historical Use of Chromium in the United States and Western World

Use	1996 Western world	1996 United States	1951 United States
Wood preservation	15%	52%	2%
Leather tanning	40%	13%	20%
Metals finishing	17%	13%	25%
Pigments	15%	12%	35%
Refractory	3%	3%	1%
Other	10%	7%	17%

Source: Barnhart 1997

5.4 DISPOSAL

Information regarding the disposal of finished products and wastes produced during the manufacturing of consumable items that contain chromium is limited. In 1987, 25% of the chromium demand in the United States was supplied by recycled stainless steel scrap. Although a large portion of the chromium wastes from plating operations is also recovered, large amounts of chromium-containing waste waters from plating, finishing, and textile industries are discharged into surface waters. A substantial amount of chromium enters sewage treatment plants from industrial and residential sources (Klein et al. 1974; TRI06 2008). Presently, slag from roasting/leaching of chromite ore is one of the materials excluded from regulation under the Resource Conservation and Recovery Act by the 1980 Bevill Amendment. However, emission control dust or sludge from ferrochromium and ferrochromium-silicon production is listed as hazardous waste by EPA (1988b). Land filling appears to be the most important method for the disposal of chromium wastes generated by chemical industries. Of the total chromium released in the environment by chemical industries, approximately 82.3% is released on land. An equally large amount of chromium waste is transferred off-site (see Section 5.2). It is anticipated that most of this off-site waste will be disposed of in landfills after proper treatment. It is important to convert chromium wastes into forms of chromium that have low mobilities in soils and low availabilities to plants and animals before land disposal. Chromium(III) oxide is one such form. Chromium in chemical industry wastes occurs predominantly in the hexavalent form. The treatment of chromium(VI) waste often involves reduction to chromium(III) and precipitation as the hydrous oxide with lime or caustic soda. Chromium(III) waste can also be converted into hydrous oxide or may be incinerated to form the oxide before land disposal. There is not much known about the disposal method of waste refractory materials used as lining for metallurgical furnaces or the disposal practices for the finished products containing chromium, such as chromium-containing pigments (Fishbein 1981; Komori et al. 1990a; NRCC 1976; Polprasert and Charnpratheap 1989; Westbrook 1979).

Chromium is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing chromium is controlled by a number of federal regulations (see Chapter 8).

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6. POTENTIAL FOR HUMAN EXPOSURE

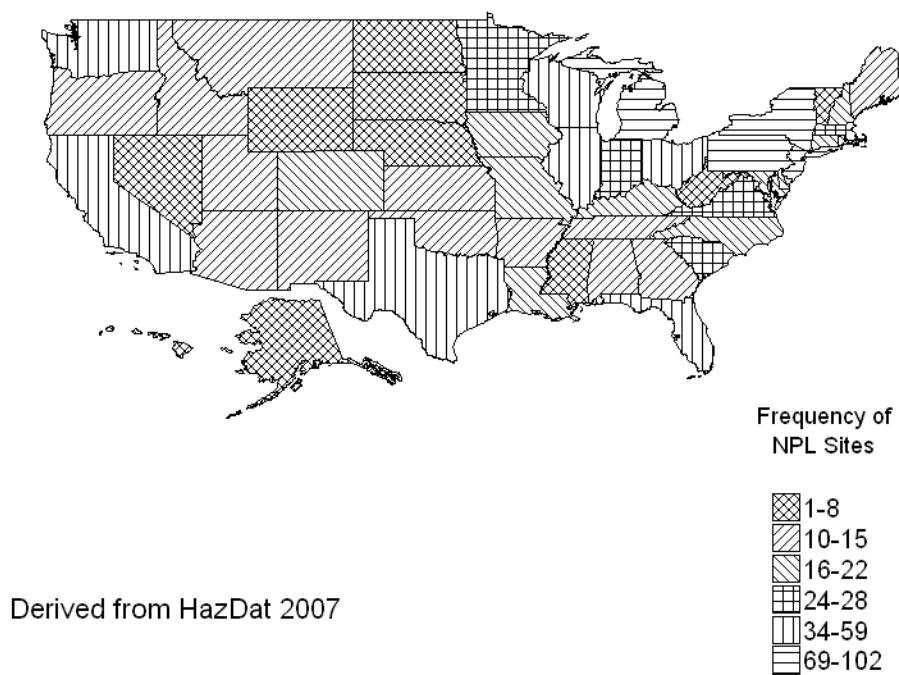
6.1 OVERVIEW

Chromium has been identified in at least 1,127 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for chromium is not known. The frequency of these sites can be seen in [Figure 6-1](#). Of these sites, 1,117 are located within the United States and 10 are located in the Commonwealth of Puerto Rico (not shown).

Human exposure to chromium occurs from both natural and anthropogenic sources. Chromium is present in the Earth's crust, with the main natural source of exposure being continental dust present in the environment (Barnhart 1997; Fishbein 1981; Pellerin and Booker 2000). Chromium is released into the environment in larger amounts as a result of human activities, which account for 60–70% of the total emissions of atmospheric chromium (Alimonti et al. 2000; Barceloux 1999; Seigneur and Constantinous 1995). This is indicated by the value of the enrichment factor (the enrichment factor relates the amount of chromium relative to an aluminum standard) of 3.5–8.1 (Dasch and Wolff 1989; Milford and Davidson 1985). Elements with enrichment factors >1 are assumed to have originated from anthropogenic sources (Schroeder et al. 1987). Of the estimated 2,700–2,900 tons of chromium emitted to the atmosphere annually from anthropogenic sources in the United States, approximately one-third is in the hexavalent form (EPA 1990b; Johnson et al. 2006). Industrial releases to the air, water, and soil are also potential sources of chromium exposure, and account for the majority of the anthropogenic releases (Johnson et al. 2006). The electroplating, leather tanning, and textile industries release large amounts of chromium to surface waters (Avudainayagam et al. 2003; Fishbein 1981; Johnson et al. 2006). Disposal of chromium-containing commercial products and coal ash from electric utilities and other industries are major sources of chromium releases into the soil (Barceloux 1999; Nriagu and Pacyna 1988). Solid waste and slag produced during chromate manufacturing processes when disposed of improperly in landfills can be potential sources of chromium exposure as well (Barceloux 1999; Kimbrough et al. 1999).

Chromium is primarily removed from the atmosphere by fallout and precipitation. The residence time of chromium in the atmosphere has not been directly measured, but by using copper as a model, it is expected to be <10 days (Nriagu 1979). The arithmetic mean concentrations of total chromium in the ambient air in United States, urban, suburban, and rural areas monitored during 1977–1984 ranged from 5 to 525 ng/m³, with the vast majority of samples <100 ng/m³ (EPA 1984a, 1990b). Ambient air in the United States usually contains very little chromium; at most measuring stations, the concentration was

6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with Chromium Contamination

6. POTENTIAL FOR HUMAN EXPOSURE

<300 ng/m³ and median levels were <20 ng/m³. As a result of smoking, indoor air contaminated with chromium can be 10–400 times greater than outdoor air concentrations (WHO 2003).

Chromium in the aquatic phase occurs in the soluble state or as suspended solids adsorbed onto clayish materials, organics, or iron oxides. Most of the soluble chromium is present as chromium(VI) or as soluble chromium(III) complexes and generally accounts for a small percentage of the total. Soluble chromium(VI) may persist in some bodies of water, but will eventually be reduced to chromium(III) by organic matter or other reducing agents in water (Cary 1982; EPA 1984a; Lide 1998). The residence times of chromium (total) in lake water range from 4.6 to 18 years, with the majority of the chromium in lakes and rivers ultimately deposited in the sediments (Schmidt and Andren 1984). In the United States, chromium concentrations are up to 84 µg/L in surface water and 0.2–1 µg/L in rainwater (WHO 2003). Most drinking water supplies in the United States contain <5 µg/L of chromium (WHO 2003). In ocean water, the mean chromium concentration is 0.3 µg/L (Cary 1982). In the United States, the groundwater concentration of chromium is generally low, with measurements in the range of 2–10 µg/L in shallow groundwater; levels as high as 50 µg/L have been reported in some supplies (WHO 2003).

Total chromium concentrations in U.S. soils range from 1 to 2,000 mg/kg, with a mean of 37.0 mg/kg (USGS 1984). Chromium(III) in soil is mostly present as insoluble carbonate and oxide of chromium(III); therefore, it will not be mobile in soil. The solubility of chromium(III) in soil and its mobility may increase due to the formation of soluble complexes with organic matter in soil, with a lower soil pH potentially facilitating complexation (Avudainayagam et al. 2003). Chromium has a low mobility for translocation from roots to the aboveground parts of plants (Calder 1988; Cary 1982; EPA 1984a, 1985a; King 1988; Stackhouse and Benson 1989).

A common source of chromium exposure is from food. Total chromium levels in most foods typically range from <10 to 1,300 µg/kg, with the highest concentrations being found in meat, fish, fruits, and vegetables (WHO 2003). The general population is exposed to chromium by inhaling air, drinking water, or eating food or food supplements that contain chromium. However, the primary source of exposure for the general population and non-occupationally exposed workers to chromium comes from food sources, although drinking water can contribute significantly when the levels are >25 µg/L (WHO 2003).

Dermal exposure to chromium may also occur during the use of consumer products that contain chromium, such as fertilizer, wood treated with copper dichromate or chromated copper arsenate, and leather tanned with chromic sulfate. In addition, people who reside in the vicinity of chromium waste

disposal sites and chromium manufacturing and processing plants have a greater probability of elevated chromium exposure (Pellerin and Booker 2000).

Exposure to chromium for occupational groups can be two orders of magnitude higher than the exposure to the general population (Hemminki and Vainio 1984). Occupational exposure to chromium occurs mainly from chromate production, stainless steel production and welding, chrome plating, production of ferrochrome alloys, chrome pigment production and user industries, and from working in tanning industries (Pellerin and Booker 2000; Stern 1982)

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 512,134 pounds of chromium to the atmosphere from 2,011 domestic manufacturing and processing facilities in 2009, accounted for about 6.6% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). Estimated releases of 269,599 pounds of chromium compounds to the atmosphere from 1,334 domestic manufacturing and processing facilities in 2009, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). These releases are summarized in [Tables 6-1 and 6-2](#).

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Metallic Chromium^a

Reported amounts released in pounds per year ^b									
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AL	45	3,708	565	0	32,551	37,542	7,720	66,646	74,366
AK	1	0	0	25,000	27,000	0	52,000	0	52,000
AZ	20	1,055	91	0	345,591	17,749	334,967	29,520	364,487
AR	25	5,067	280	0	4,070	250	5,078	4,589	9,667
CA	85	1,653	1,287	382	11,059	11,749	1,674	24,457	26,131
CO	21	290	29	0	28,935	27,412	27,627	29,039	56,666
CT	45	542	2,060	0	15,242	36,845	10,913	43,777	54,689
DE	2	5	0	0	334	0	5	334	339
FL	29	90	31	0	255,926	1,889	188,645	69,290	257,935
GA	44	1,003	396	0	47,228	1,886	1,320	49,193	50,513
ID	5	105	0	0	130,286	487	107,517	23,361	130,879
IL	109	4,982	26,157	0	24,175	17,870	5,012	68,172	73,184
IN	119	15,813	3,811	0	1,490,024	85,846	29,247	1,566,247	1,595,493
IA	43	2,183	65	0	61,992	109,972	2,245	171,968	174,213
KS	40	8,066	217	0	3,330	270	8,088	3,795	11,883
KY	49	7,123	623	0	22,447	9,475	7,222	32,446	39,668
LA	35	1,367	232	0	49,357	164	17,636	33,484	51,121
ME	8	88	122	0	43	2,970	88	3,134	3,222
MD	7	1	14	0	9	11	1	34	35
MA	34	1,026	350	0	12,580	10,706	1,281	23,380	24,662
MI	78	7,673	2,382	0	25,049	4,951	8,729	31,326	40,055
MN	38	2,163	39	0	7,146	69	2,163	7,255	9,418
MS	22	2,806	12	0	454	72	2,808	536	3,344
MO	37	298,980	513	0	4,206	76	298,995	4,781	303,775
MT	1	0	0	0	520,172	0	520,172	0	520,172
NE	11	809	257	0	82,754	75	46,541	37,354	83,895
NV	14	238	6,631	0	1,080,422	407	1,076,822	10,876	1,087,699
NH	15	126	45	0	26	1,125	126	1,195	1,321
NJ	21	440	17	0	26,248	141	448	26,398	26,846
NM	3	52	0	0	54	0	106	0	106
NY	49	4,612	6,544	0	48,786	880	19,512	41,309	60,821
NC	52	928	312	0	4,008	6,969	976	11,241	12,217
ND	5	21	9	0	10,453	0	10,236	247	10,483
OH	164	9,119	5,675	0	204,658	73,201	43,141	249,513	292,654
OK	66	2,389	59	0	6,561	1,551	2,394	8,167	10,560

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Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Metallic Chromium^a

Reported amounts released in pounds per year ^b										
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release			
							On-site ^j	Off-site ^k	On- and off-site	
OR	14	2,726	43		0	73,071	24	70,154	5,710	75,864
PA	180	12,514	1,378		0	658,699	217,491	47,732	842,350	890,082
PR	5	29	0		0	20	0	29	20	49
RI	5	0	0		0	0	1	0	1	1
SC	51	6,009	2,892		0	99,752	868	6,103	103,417	109,520
SD	8	45	1		0	42,240	1	42,162	125	42,287
TN	49	1,629	837		0	57,445	13,005	1,900	71,017	72,917
TX	140	6,499	8,912	213,649		20,672	5,244	221,563	33,414	254,976
UT	18	624	10		0	27,087	3,726	19,141	12,308	31,448
VT	4	22	13		0	32	215	27	255	282
VA	22	172	20,799		0	49,635	396	19,270	51,733	71,002
WA	21	1,608	142		0	48,867	4,633	2,864	52,386	55,249
WV	7	2,984	706		0	14,833	501	2,991	16,034	19,024
WI	142	92,652	4,452		0	476,398	27,955	93,201	508,256	601,456
WY	3	95	2		0	41,823	176	41,892	204	42,096
Total	2,011	512,134	99,011	239,031	6,193,750	736,849	3,410,482	4,370,293	7,780,775	

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI09 2011 (Data are from 2009)

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Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds^a

Reported amounts released in pounds per year ^b									
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AK	4	192	10	0	1,051,055	0	1,051,257	0	1,051,257
AL	41	12,995	3,368	0	855,643	33,148	756,162	148,992	905,154
AR	25	1,830	209	0	89,381	51,460	61,330	81,549	142,880
AZ	19	1,876	42	0	1,462,139	1,739	1,460,380	5,416	1,465,796
CA	42	699	17,437	0	252,991	58,991	190,150	139,969	330,119
CO	11	510	15	0	394,416	250	346,695	48,496	395,191
CT	13	1,305	820	0	16,344	20,567	1,328	37,707	39,035
DE	4	208	297	0	508,021	0	27,157	481,369	508,526
FL	25	4,306	357	0	385,025	22,394	346,871	65,211	412,082
GA	41	6,050	3,428	0	560,164	4,984	549,328	25,298	574,625
HI	1	0	0	0	0	0	.	.	.
IA	15	7,476	50	0	146,295	110	74,254	79,676	153,930
ID	1	5,922	4	0	464,262	5	470,188	5	470,194
IL	72	5,913	19,980	636	949,161	164,644	219,738	920,596	1,140,334
IN	76	17,409	196,624	900	2,128,495	693,344	1,490,246	1,546,525	3,036,771
KS	23	6,121	2,902	250	368,352	213,474	106,741	484,358	591,099
KY	45	21,332	9,012	0	2,670,506	44,468	972,602	1,772,715	2,745,318
LA	21	1,229	440	1	260,204	16,688	214,862	63,700	278,562
MA	11	538	6	0	28,267	15,101	617	43,295	43,911
MD	21	2,401	532	0	110,310	144,631	74,943	182,931	257,873
ME	6	133	450	0	31,822	71,378	543	103,240	103,783
MI	73	10,157	9,079	4,400	557,893	16,191	340,219	257,502	597,720
MN	25	1,573	14,278	0	127,028	15,383	75,650	82,612	158,261
MO	26	4,537	618	0	336,752	37,987	104,979	274,916	379,894
MS	33	3,277	1,026	2,297,309	1,008,735	32,026	3,168,752	173,623	3,342,374
MT	8	1,805	0	0	250,394	645	102,190	150,653	252,843
NC	42	7,004	39,737	0	1,299,616	16,645	1,183,540	179,461	1,363,001
ND	7	4,869	242	0	289,934	1,533	134,352	162,226	296,578
NE	11	3,629	2,770	0	84,154	5,697	75,712	20,538	96,251
NH	3	69	10	0	10,650	250	2,079	8,900	10,979
NJ	17	1,590	39,946	0	3,865	52,021	3,765	93,658	97,423
NM	4	659	0	0	180,656	0	181,315	0	181,315
NV	7	255	0	0	1,531,094	0	1,531,349	0	1,531,349
NY	21	898	1,103	0	64,214	1,238	32,491	34,962	67,453
OH	101	28,059	17,971	444,822	2,125,297	247,620	1,578,830	1,284,938	2,863,768

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Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Chromium Compounds^a

Reported amounts released in pounds per year ^b										
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release			
							On-site ^j	Off-site ^k	On- and off-site	
OK	19	3,389	306		0	465,657	3,844	444,881	28,315	473,196
OR	11	235	106		0	58,134	653	7,961	51,167	59,128
PA	113	50,601	15,177		0	2,004,874	235,591	818,001	1,488,242	2,306,243
PR	7	5,285	51		0	3,193	198	5,285	3,443	8,728
RI	5	0	0		0	300	0	0	300	300
SC	2	3,260	2,945		0	389,283	130,685	278,206	247,966	526,172
SD	27	13	8		0	0	0	13	8	20
TN	3	4,604	30,074		0	2,109,366	5,918	1,570,982	578,980	2,149,962
TX	43	16,668	3,020	31,886	1,316,207	110,630	1,283,443	194,969	1,478,412	1,478,412
UT	92	2,088	1,262		0	1,632,406	14,465	1,538,140	112,081	1,650,221
VA	15	1,002	6,116		0	171,669	359	163,200	15,947	179,146
WA	16	568	36,434		0	75,005	106,290	43,057	175,240	218,298
WI	23	6,195	4,745		0	204,646	68,916	11,886	272,616	284,502
WV	16	4,465	2,878		0	911,062	29,786	603,016	345,175	948,191
WY	47	4,399	180		0	211,926	636	190,665	26,476	217,141
Total	1,334	269,599	486,063	2,780,204	30,156,862	2,692,585	23,889,351	12,495,962	36,385,312	36,385,312

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI09 2011 (Data are from 2009)

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Total chromium has been identified in air samples at 48 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

Continental dust flux is the main natural source of chromium in the atmosphere; volcanic dust and gas flux are minor natural sources of chromium in the atmosphere (Fishbein 1981). Chromium is released into the atmosphere mainly by anthropogenic stationary point sources, including industrial, commercial, and residential fuel combustion, *via* the combustion of natural gas, oil, and coal (Kimbrough et al. 1999; Pacyn and Pacyn 2001; Seigneur and Constantinous 1995). Other important anthropogenic stationary point sources of chromium emission to the atmosphere are metal industries, such as chrome plating and steel production (EPA 1990b; Johnson et al. 2006; Pacyn and Pacyn 2001). Approximately one-third of the atmospheric releases of chromium are believed to be in the hexavalent form, chromium(VI) (Johnson et al. 2006). Other potentially small sources of atmospheric chromium emission are cement-producing plants (cement contains chromium), the wearing down of asbestos brake linings that contain chromium, incineration of municipal refuse and sewage sludge, and emission from chromium-based automotive catalytic converters. Emissions from cooling towers that previously used chromate chemicals as rust inhibitors are also atmospheric sources of chromium (EPA 1984b, 1990b; Fishbein 1981).

6.2.2 Water

Estimated releases of 99,011 pounds of chromium to surface water from 2,011 domestic manufacturing and processing facilities in 2009, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). Estimated releases of 486,063 pounds of chromium compounds to surface water from 1,334 domestic manufacturing and processing facilities in 2009, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011).

Total chromium has been identified in surface water and groundwater samples at 427 of 1,699 and 813 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

On a worldwide basis, the major chromium source in aquatic ecosystems is domestic waste water effluents (32.2% of the total) (Barceloux 1999). The other major sources are metal manufacturing (25.6%), ocean dumping of sewage (13.2%), chemical manufacturing (9.3%), smelting and refining of nonferrous metals (8.1%), and atmospheric fallout (6.4%) (Nriagu and Pacyna 1988). Annual

anthropogenic input of chromium into water has been estimated to exceed anthropogenic input into the atmosphere (Nriagu and Pacyna 1988). However, land erosion, a natural source of chromium in water, was not included in the Nriagu and Pacyna (1988) estimation of chromium contributions to the aquatic environment.

6.2.3 Soil

Estimated releases of 6,193,750 pounds of chromium to soils from 2,011 domestic manufacturing and processing facilities in 2009, accounted for about 80% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). An additional 239,031 pounds of chromium were released via underground injection. Estimated releases of 30,156,862 pounds of chromium compounds to soils from 1,334 domestic manufacturing and processing facilities in 2009, accounted for about 83% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). An additional 2,780,204 pounds were released via underground injection. These releases are summarized in [Tables 6-1 and 6-2](#).

Total chromium has been identified in soil and sediment samples at 696 of 1,699 and 471 of 1,699 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

On a worldwide basis, the disposal of commercial products that contain chromium may be the largest contributor, accounting for 51% of the total chromium released to soil (Nriagu and Pacyna 1988). Other significant sources of chromium release into soil include the disposal of coal fly ash and bottom fly ash from electric utilities and other industries (33.1%), agricultural and food wastes (5.3%), animal wastes (3.9%), and atmospheric fallout (2.4%) (Nriagu and Pacyna 1988). Solid wastes from metal manufacturing constituted <0.2% to the overall chromium release in soil. However, the amount of chromium in sludge or residue that is disposed of in landfills by manufacturing and user industries that treat chromate wastes in ponds and lagoons is not included in the estimation by Nriagu and Pacyna (1988).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Chromium is present in the atmosphere primarily in particulate form; naturally occurring gaseous forms of chromium are rare (Cary 1982; Kimbrough et al. 1999; Seigneur and Constantinos 1995). The

transport and partitioning of particulate matter in the atmosphere depends largely on particle size and density. Atmospheric particulate matter is deposited on land and water via wet and dry deposition. Wet, dry, and total deposition rates of chromium and several other trace metals in remote, rural and urban areas were summarized by Schroeder et al. (1987). Deposition rates tended to be highest in urban areas that had greater atmospheric levels of chromium as compared to rural and remote locations. The rates of wet and dry deposition are dependent upon several factors, including particle and aerosol size distribution (Kimbrough et al. 1999). The mass mean aerodynamic diameter (MMAD) of chromium aerosols or particulates emitted from several industrial sources are $\leq 10 \mu\text{m}$ and it has been estimated that chromium-containing particulates emitted from these industrial sources can remain airborne for 7–10 days and are subject to long-range transport (Kimbrough et al. 1999). Based on a troposphere to stratosphere turnover time of 30 years (EPA 1979), atmospheric particles with a residence time of <10 days are not expected to transport from the troposphere to the stratosphere and there are no data in the reviewed literature indicating that chromium particles are transported from the troposphere to the stratosphere (Pacyna and Ottar 1985).

Since chromium compounds cannot volatilize from water, transport of chromium from water to the atmosphere is not likely, except by transport in windblown sea sprays. Most of the chromium released into water will ultimately be deposited in the sediment. A very small percentage of chromium in the water column is present in both soluble and insoluble forms. In the aquatic phase, chromium(III) occurs mostly as suspended solids adsorbed onto clayish materials, organics, or iron oxide (Fe_2O_3) present in water. Approximately 10.5–12.6% of chromium in the aquatic phase of the Amazon and Yukon Rivers was in solution, the rest being present in the suspended solid phase (Cary 1982; King 1988). The ratio of chromium in suspended solids to dissolved form in an organic-rich river in Brazil was 2.1 (Malm et al. 1988).

The bioconcentration factor (BCF) for chromium(VI) in rainbow trout (*Salmo gairdneri*) is 1. In bottom-feeder bivalves, such as the oyster (*Crassostrea virginica*), blue mussel (*Mytilus edulis*), and soft shell clam (*Mya arenaria*), the BCF values for chromium(III) and chromium(VI) range from 86 to 192 (EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984). The bioavailability of chromium(III) to freshwater invertebrates (*Daphnia pulex*) decreased with the addition of humic acid (Ramelow et al. 1989). This decrease in bioavailability was attributed to lower availability of the free form of the metal due to its complexation with humic acid. Based on this information, chromium is not expected to biomagnify in the aquatic food chain. Although higher concentrations of chromium have been reported in plants growing in high chromium-containing soils (e.g., soil near ore deposits or chromium-emitting

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industries and soil fertilized by sewage sludge) compared with plants growing in normal soils, most of the increased uptake in plants is retained in roots, and only a small fraction is translocated in the aboveground part of edible plants (Cary 1982; WHO 1988). Therefore, bioaccumulation of chromium from soil to aboveground parts of plants is unlikely (Petrizzelli et al. 1987). There is no indication of biomagnification of chromium along the terrestrial food chain (soil-plant-animal) (Cary 1982).

The mobility of chromium in soil is dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) oxidation state. This form has very low solubility and low reactivity, resulting in low mobility in the environment (Barnhart 1997; Jardine et al. 1999; Robson 2003). Under oxidizing conditions, chromium(VI) may be present in soil as CrO_4^{2-} and HCrO_4^- (James et al. 1997). In this form, chromium is relatively soluble and mobile. A leachability study comparing the mobility of several metals, including chromium, in soil demonstrated that chromium had the least mobility of all of the metals studied (Sahuquillo et al. 2003). These results support previous data finding that chromium is not very mobile in soil, especially in the trivalent oxidation state (Balasoiu et al. 2001; Jardine et al. 1999; Lin et al. 1996; Robson 2003). These results are further supported by a leachability investigation in which chromium mobility was studied for a period of 4 years in a sandy loam (Sheppard and Thibault 1991). The vertical migration pattern of chromium in this soil indicated that after an initial period of mobility, chromium forms insoluble complexes and little leaching is observed. Chromium present as insoluble oxide, $\text{Cr}_2\text{O}_3 \cdot n\text{H}_2\text{O}$, exhibited limited mobility in soil (Rifkin et al. 2004). Flooding of soils and the subsequent anaerobic decomposition of plant detritus matters may increase the mobilization of chromium(III) in soils due to formation of soluble complexes (Stackhouse and Benson 1989). This complexation may be facilitated by a lower soil pH.

A smaller percentage of total chromium in soil exists as soluble chromium(VI) and chromium(III) complexes, which are more mobile in soil. Chromium that is irreversibly sorbed onto soil (e.g., in the interstitial lattice of goethite, FeOOH) will not be bioavailable to plants and animals under any condition. Organic matter in soil is expected to convert soluble chromate, chromium(VI), to insoluble chromium(III) oxide, Cr_2O_3 (Calder 1988). Surface runoff from soil can transport both soluble and bulk precipitate of chromium to surface water. Soluble and unadsorbed chromium(VI) and chromium(III) complexes in soil may leach into groundwater. The leachability of chromium(VI) in the soil increases as the pH of the soil increases. On the other hand, lower pH present in acid rain may facilitate leaching of acid-soluble chromium(III) complexes and chromium(VI) compounds in soil. Chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary 1982). However, depending on the

geographical areas where the plants are grown, the concentration of chromium in aerial parts of certain plants may differ by a factor of 2–3 (Cary 1982).

6.3.2 Transformation and Degradation

6.3.2.1 Air

In the atmosphere, chromium(VI) may be reduced to chromium(III) at a significant rate by vanadium (V^{2+} , V^{3+} , and VO^{2+}), Fe^{2+} , HSO_3^- , and As^{3+} (EPA 1987b; Kimbrough et al. 1999). Conversely, chromium(III), if present as a salt other than Cr_2O_3 , may be oxidized to chromium(VI) in the atmosphere if 1% of the manganese in atmospheric aerosols is present as MnO_2 (EPA 1990b). The estimated atmospheric half-life for chromium(VI) reduction to chromium(III) was reported in the range of 16 hours to about 5 days (Kimbrough et al. 1999).

6.3.2.2 Water

The reduction of chromium(VI) to chromium(III) and the oxidation of chromium(III) to chromium(VI) in water has been investigated extensively. Reduction of chromium(VI) to chromium(III) can occur under suitable conditions in the aqueous environment, if an appropriate reducing agent is available. The most common reducing agents present in aqueous systems include: organic matter; hydrogen sulfide; sulfur, iron sulfide; ammonium; and nitrate (Kimbrough et al. 1999). The reduction of chromium(VI) by S^{2-} or Fe^{+2} ions under anaerobic conditions occurs rapidly, with the reduction half-life ranging from instantaneous to a few days (Seigneur and Constantinos 1995). However, the reduction of chromium(VI) by organic sediments and soils was much slower and depended on the type and amount of organic material and on the redox condition of the water. The reduction half-life of chromium(VI) in water with soil and sediment ranged from 4 to 140 days, with the reaction typically occurring faster under anaerobic rather than aerobic conditions (Saleh et al. 1989). Generally, the reduction of chromium(VI) to chromium(III) is also favored under acidic conditions (Kimbrough et al. 1999).

Oxidation of chromium(III) to chromium(VI) can also occur in the aqueous environment, depending on several factors. Although oxygen is known to oxidize chromium(III) to chromium(VI), dissolved oxygen by itself in natural waters did not cause any measurable oxidation of chromium(III) to chromium(VI) over a period of 128 days (Saleh et al. 1989). When chromium(III) was added to lake water, a slow oxidation of chromium(III) to chromium(VI) occurred, corresponding to an oxidation half-life of nine years. Addition of 50 mg/L manganese oxide accelerated the process, decreasing the oxidation half-life to

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approximately 2 years (Saleh et al. 1989). The oxidation of chromium(III) to chromium(VI) during chlorination of water was highest in the pH range of 5.5–6.0 (Saleh et al. 1989). However, the process would rarely occur during chlorination of drinking water because of the low concentrations of chromium(III) in these waters, and the presence of naturally occurring organics that may protect chromium(III) from oxidation, either by forming strong complexes with chromium(III) or by acting as a reducing agent to free available chlorine (EPA 1988c). In chromium(III)-contaminated waste waters having pH ranges of 5–7, chlorination may convert chromium(III) to chromium(VI) in the absence of chromium(III)-complexing and free chlorine reducing agents (EPA 1988c).

Chromium speciation in groundwater also depends on the redox potential and pH conditions in the aquifer. Chromium(VI) predominates under highly oxidizing conditions; whereas chromium(III) predominates under reducing conditions. Oxidizing conditions are generally found in shallow, oxygenated aquifers, and reducing conditions generally exist in deeper, anaerobic groundwaters. In natural groundwater, the pH is typically 6–8, and CrO_4^{2-} is the predominant species of chromium in the hexavalent oxidation state, while $\text{Cr}(\text{OH})_2^{+1}$ will be the dominant species in the trivalent oxidation state. This species and other chromium(III) species will predominate in more acidic pH; $\text{Cr}(\text{OH})_3$ and $\text{Cr}(\text{OH})_4^{-1}$ predominate in more alkaline waters (Calder 1988).

6.3.2.3 Sediment and Soil

The fate of chromium in soil is greatly dependent upon the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the chromium(III) state. This form has very low solubility and low reactivity resulting in low mobility in the environment and low toxicity in living organisms (Ashley et al. 2003; Barnhart 1997; EPA 1994b). Under oxidizing conditions, chromium(VI) may be present in soil as CrO_4^{2-} and HCrO_4^- (James et al. 1997). In this form, chromium is relatively soluble, mobile, and toxic to living organisms. In deeper soil where anaerobic conditions exist, chromium(VI) will be reduced to chromium(III) by S^{2-} and Fe^{+2} present in soil. The reduction of chromium(VI) to chromium(III) is possible in aerobic soils that contain appropriate organic energy sources to carry out the redox reaction, with the reduction of chromium(VI) to chromium(III) facilitated by low pH (Cary 1982; EPA 1990b; Saleh et al. 1989).

The oxidation of chromium(III) to chromium(VI) in soil is facilitated by the presence of organic substances, oxygen, manganese dioxide, moisture, and the elevated temperatures in surface soil that result from brush fires (Calder 1988; Cary 1982). Organic forms of chromium(III) (e.g., humic acid complexes)

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are more easily oxidized than insoluble oxides. However, oxidation of chromium(III) to chromium(VI) was not observed in soil under conditions of maximum aeration and a maximum pH of 7.3 (Bartlett and Kimble 1976). It was later reported that soluble chromium(III) in soil can be partly oxidized to chromium(VI) by manganese dioxide in soil, and the process is enhanced at pH values >6 (Bartlett 1991). Because most chromium(III) in soil is immobilized due to adsorption and complexation with soil materials, the barrier to this oxidation process is the lack of availability of mobile chromium(III) to immobile manganese dioxide in soil surfaces. Due to this lack of availability of mobile chromium(III) to manganese dioxide surfaces, a large portion of chromium in soil will not be oxidized to chromium(VI), even in the presence of manganese dioxide and favorable pH conditions (Bartlett 1991; James et al. 1997).

The microbial reduction of chromium(VI) to chromium(III) has been discussed as a possible remediation technique in heavily contaminated environmental media or wastes (Chen and Hao 1998; EPA 1994b). Factors affecting the microbial reduction of chromium(VI) to chromium(III) include biomass concentration, initial chromium(VI) concentration, temperature, pH, carbon source, oxidation-reduction potential, and the presence of both oxyanions and metal cations. Although high levels of chromium(VI) are toxic to most microbes, several resistant bacterial species have been identified that could ultimately be employed in remediation strategies (Chen and Hao 1998; EPA 1994b). Elemental iron, sodium sulfite, sodium hydrosulfite, sodium bisulfite, sodium metabisulfite sulfur dioxide, and certain organic compounds such as hydroquinone have also been shown to reduce chromium(VI) to chromium(III) and have been discussed as possible remediation techniques in heavily contaminated soils (Higgins et al. 1997; James et al. 1997). The limitations and efficacy of these and all remediation techniques are dependent upon the ease in which the reducing agents are incorporated into the contaminated soils.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chromium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of chromium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on chromium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring chromium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Levels of total chromium in the ambient air in U.S. urban and nonurban areas during 1977–1984 are reported in EPA's National Aerometric Data Bank (EPA 1984a, 1990b). According to this databank, the arithmetic mean total chromium concentrations from a total of 2,106 monitoring stations ranged from 5 to 525 ng/m³. The two locations that showed the highest total arithmetic mean chromium concentrations were in Steubenville, Ohio, in 1977 (525 ng/m³) and in Baltimore, Maryland, in 1980 (226 ng/m³) (EPA 1990b). Arithmetic mean total chromium concentrations in only 8 of 173 sites monitored in 1984 were >100 ng/m³ (EPA 1990b).

An indoor/outdoor air study was conducted in southwestern Ontario to measure levels of chromium(VI) and the size fraction of chromium(VI). Indoor and outdoor samples were taken from 57 homes during the summer months of 1993. The concentrations were 0.1–0.6 ng/m³ indoors (geometric mean 0.2 ng/m³) and were 0.10–1.6 ng/m³ outdoors (geometric mean 0.55 ng/m³). The indoor concentrations were less than half of the outdoor concentrations. Analysis of airborne chromium(VI) particles showed that they were inhalable in size (Bell and Hipfner 1997). A study measured the levels of chromium(VI) and total chromium in the ambient air in Hudson County, New Jersey. The concentrations of chromium(VI) in the indoor air of residences in Hudson County in 1990 ranged from 0.38 to 3,000 ng/m³, with a mean of 1.2 ng/m³ (Falerios et al. 1992).

Another study analyzed the relationship between soil levels of chromium and chromium content of the atmosphere. An indoor/outdoor study was conducted at 25 industrial sites in Hudson County, New Jersey to analyze soils containing chromite ore processing residues. The industrial sites include industrial, manufacturing, trucking, and warehouse facilities. The study found industrial indoor chromium(VI) and total chromium concentrations to be 0.23–11 and 4.1–130 ng/m³ and industrial outdoor chromium(VI) and total chromium concentrations to be 0.013–15.3 and 1.9–84.5 ng/m³. The results of this study found that higher levels of chromium(VI) in soil do not necessarily result in higher levels of chromium(VI) in air (Finley et al. 1993). The mean concentration of total chromium at the same sites was 7.1 ng/m³, with a concentration range of 3.7–12 ng/m³. Monitoring data in Hudson County, New Jersey has shown a background chromium(VI) concentration of 0.2–3.8 ng/m³ with a mean concentration of 1.2 ng/m³ (Scott et al. 1997a). The airborne total chromium concentration range was 1.5–10 ng/m³ with a mean concentration of 4.5 ng/m³ (Scott et al. 1997a). The mean airborne chromium(VI) and total chromium concentrations in the indoor air of industrial sites in Hudson County, New Jersey, contaminated by chromite ore-processing residue were 3 ng/m³ (range, 0.23–11 ng/m³) and 23 ng/m³ (range, 4.11–

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130 ng/m³), respectively. The mean airborne chromium(VI) and total chromium concentrations in outdoor air for the same sites were 9.9 ng/m³ (range, 0.13–110 ng/m³) and 37 ng/m³ (range, 1.9–250 ng/m³), respectively (Falerios et al. 1992).

An air dispersion model was developed which accurately estimated chromium(VI) concentrations at two of these industrial sites in Hudson County, New Jersey (Scott et al. 1997b). The background corrected airborne concentrations in ng/m³ for seven sampling dates are reported as measured (modeled values in parentheses): 0.0 (0.41); 6.2 (7.7); 0.9 (1.7); 2.8 (2.7); 0.0 (0.08); 0.3 (0.1); and 1.2 (0.12). The estimated percent levels of chromium(III) and chromium(VI) in the U.S. atmosphere from anthropogenic sources are given in Table 6-3 (EPA 1990b). Fly ash from a coal-fired power plant contained 1.4–6.1 mg/kg chromium(VI) (Stern et al. 1984). In a field study to assess inhalation exposure to chromium during showering and bathing activities, the average chromium(VI) concentration in airborne aerosols ranged from 87 to 324 ng/m³ when water concentrations of 0.89–11.5 mg/L of chromium(VI) were used in a standard house shower (Finley et al. 1996a).

The concentrations of atmospheric chromium in remote areas, such as the Arctic region and the South Pole, range from 0.005 to 2.6 ng/m³ (Barrie and Hoff 1985; Cary 1982; Schroeder et al. 1987; Sheridan and Zoller 1989). Saltzman et al. (1985) compared the levels of atmospheric chromium at 59 sites in U.S. cities during 1968–1971 with data from EPA's National Aerometric Data Bank file for 1975–1983. They concluded that atmospheric chromium levels may have declined in the early 1980s from the levels detected in the 1960s and 1970s.

6.4.2 Water

Chromium concentrations in U.S. river water usually range from <1 to 30 µg/L (EPA 1984a; Malm et al. 1988; Ramelow et al. 1987), with a median value of 10 µg/L (Eckel and Jacob 1988; Smith et al. 1987). Chromium concentrations in lake water generally do not exceed 5 µg/L (Borg 1987; Cary 1982), with higher levels of chromium related to anthropogenic pollution sources. Dissolved chromium concentrations of 0.57–1.30 µg/L were reported in the Delaware River near Marcus Hook and Fieldsboro, Pennsylvania in January 1992, with chromium(III) composing 67% of the total (Riedel and Sanders 1998). In March 1992, these concentrations decreased to 0.03–0.23 µg/L. In general, the concentration of chromium in ocean water is much lower than that in lakes and rivers. The mean chromium concentration in ocean water is 0.3 µg/L, with a range of 0.2–50 µg/L (Cary 1982). The mean concentration of chromium in rainwater is 0.14–0.9 µg/L (Barrie et al. 1987; Dasch and Wolff 1989).

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Table 6-3. Estimates of U.S. Atmospheric Chromium Emissions from Anthropogenic Sources

Source category	Estimated number of sources	Chromium emissions (metric tons/year)	Estimated hexavalent chromium (percent)
Combustion of coal and oil	Many	1,723	0.2
Chromium chemical manufacturing	2	18	67
Chemical manufacturing cooling towers	2,039	43	100
Petroleum refining cooling towers	475	32	100
Specialty/steel production	18	103	2.2
Primary metal cooling towers	224	8	100
Chrome plating	4,000	700	~100
Comfort cooling towers	38,000	7.2–206	100
Textile manufacturing cooling towers	51	0.1	100
Refractory production	10	24	1.3
Ferrochromium production	2	16	5.4
Sewage sludge incineration	133	13	<0.1
Tobacco cooling towers	16	0.2	100
Utility industry cooling towers	6	1.0	100
Chrome ore refining	6	4.8	<0.1
Tire and rubber cooling towers	40	0.2	100
Glass manufacturing cooling towers	3	0.01	100
Cement production	145	3	0.2
Municipal refuse incineration	95	2.5	0.3
National total		2,700–2,900	

Source: EPA 1990b

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The concentrations of total chromium in groundwater at the Idaho National Engineering Laboratory, where chromate is used as a corrosion inhibitor, ranged from <1 to 280 µg/L (USGS 1989). The water from a village well situated near a waste pond receiving chromate waste in Douglas, Michigan, contained 10,800 µg/L chromium(VI). Similarly, water from a private well adjacent to an aircraft plant in Nassau County, New York, contained 25,000 µg/L chromium(VI), while water from a public well adjacent to another aircraft plant in Bethpage, New York, contained 1,400 µg/L chromium(VI) (Davids and Lieber 1951). In a later study, water from an uncontaminated well in Nassau County, New York, contained an undetectable level of chromium(VI), whereas a contaminated well in the vicinity of a plating plant contained 6,000 µg/L chromium(VI) (Lieber et al. 1964). A chromium concentration of 120 µg/L was detected in private drinking water wells adjacent to an NPL site in Galena, Kansas (Agency for Toxic Substances and Disease Registry 1990a).

The chromium levels detected in drinking water in an earlier study (1962–1967 survey) may be erroneous due to questionable sampling and analytical methods (see Section 7.1) (EPA 1984a). Total chromium levels in drinking water were reported to range from 0.2 to 35 µg/L (EPA 1984a). Most drinking water supplies in the United States contain <5 µg/L of total chromium (WHO 2003). The concentration of chromium in household tap water may be higher than supply water due to corrosion of chromium-containing pipes. At a point of maximum contribution from corrosion of the plumbing system, the peak chromium in tap water in Boston, Massachusetts was 15 µg/L (Ohanian 1986). A survey that targeted drinking waters from 115 Canadian municipalities during 1976–1977 reported the median chromium concentration to be <2.0 µg/L (detection limit) and the maximum chromium concentration to be 8.0 µg/L (Meranger et al. 1979). A recent monitoring survey of drinking water by the California Department of Public Health found that levels of chromium(VI) were <10 µg/L in 86% (2,003 out of 2,317 sources) of the drinking water sources sampled; however, levels above 50 µg/L were noted in six sources (CDPH 2007). In this survey, a source was defined as those reporting more than a single detection of chromium(VI) and may include both raw and treated sources, distribution systems, blending reservoirs, and other sampled entities. These data did not include agricultural wells, monitoring wells, or more than one representation of the same source (e.g., a source with both raw and treated entries is counted a single source).

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6.4.3 Sediment and Soil

The chromium level in soils varies greatly and depends on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks, and phosphorites may contain chromium as high as a few thousand mg/kg (Merian 1984) whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine and Mitchell 1960). The concentration range of chromium in 1,319 samples of soils and other surficial materials collected in the conterminous United States was 1–2,000 mg/kg, with a geometric mean of 37 mg/kg (USGS 1984). Chromium concentrations in Canadian soils ranged from 5 to 1,500 mg/kg, with a mean of 43 mg/kg (Cary 1982). In a study with different kinds of soils from 20 diverse sites including old chromite mining sites in Maryland, Pennsylvania, and Virginia, the chromium concentration ranged from 4.9 to 71 mg/kg (Beyer and Cromartie 1987). A polynuclear aromatic hydrocarbon (PAH) soil study was conducted to determine the metal levels in soil at the edge of a busy road that runs through the Aplerbecker Forest in West Germany. Chromium(VI) concentrations of 64 mg/kg were measured, and these concentrations were 2- to 4-fold higher along the road than in the natural forest (Munch 1993). The soil beneath decks treated with chrominated copper arsenate (CCA), a wood preservative, had an average chromium content of 43 mg/kg (Stilwell and Gorny 1997).

Chromium has been detected at a high concentration (43,000 mg/kg) in soil at the Butterworth Landfill site in Grand Rapid City, Michigan, which was a site listed on the NPL (Agency for Toxic Substances and Disease Registry 1990b).

Chromium was detected in sediment obtained from the coastal waters of the eastern U.S. seashore at concentrations of 3.8–130.9 µg/g in 1994 and 0.8–98.1 µg/g in 1995 (Hyland et al. 1998).

6.4.4 Other Environmental Media

The concentration of chromium in the particulate portion of melted snow collected from two urban areas (Toronto and Montreal) of Canada ranged from 100 to 3,500 mg/kg (Landsberger et al. 1983). In the suspended materials and sediment of water bodies, chromium levels ranged from 1 to 500 mg/kg (Byrne and DeLeon 1986; EPA 1984a; Mudroch et al. 1988; Ramelow et al. 1987). The chromium concentration in incinerated sewage sludge ash may be as high as 5,280 mg/kg (EPA 1984a).

Total chromium levels in most fresh foods are extremely low (vegetables [20–50 µg/kg], fruits [20 µg/kg], and grains and cereals [40 µg/kg]) (Fishbein 1984). The chromium levels of various foods are

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reported in Table 6-4. In a study to find the concentrations of chromium in edible vegetables in Tarragon Province, Spain, the highest levels of chromium were found in radish root and spinach, with a nonsignificant difference between the samples collected in two areas (northern industrial and southern agricultural). The samples ranged in concentration from 0.01 to 0.21 µg/g (industrial) and from 0.01 to 0.22 µg/g (agricultural) (Schuhmacker et al. 1993). Acidic foods that come into contact with stainless steel surfaces during harvesting, processing, or preparation for market are sometimes higher in chromium content because of leaching conditions. Processing, however, removes a large percentage of chromium from foods (e.g., whole-grain bread contains 1,750 µg/kg chromium, but processed white bread contains only 140 µg/kg; and molasses contains 260 µg/kg chromium, but refined sugar contains only 20 µg/kg chromium) (Anderson 1981; EPA 1984a).

Chromium levels in oysters, mussels, clams, and mollusks vary from <0.1 to 6.8 mg/kg (dry weight) (Byrne and DeLeon 1986; Ramelow et al. 1989). Fish and shellfish collected from ocean dump sites off New York City, Delaware Bay, and New Haven, Connecticut, contained <0.3–2.7 mg/kg chromium (wet weight) (Greig and Jones 1976). The chromium concentration in fish sampled from 167 lakes in the northeastern United States was 0.03–1.46 µg/g with a mean concentration of 0.19 µg/g (Yeardley et al. 1998). Higher levels of chromium in forage of meat animals have been reported for plants grown in soils with a high concentration of chromium (see Section 6.3.1). Cigarette tobacco reportedly contains 0.24–14.6 mg/kg chromium, but no estimates were available regarding the chromium levels in inhaled cigarette smoke (Langård and Norseth 1986). Cigarette tobacco grown in the United States contains ≤6.3 mg/kg chromium (IARC 1980).

Cement-producing plants are a potential source of atmospheric chromium. Portland cement contains 41.2 mg/kg chromium (range 27.5–60 mg/kg). Soluble chromium accounts for 4.1 mg/kg (range 1.6–8.8 mg/kg) of which 2.9 mg/kg (range 0.03–7.8 mg/kg) is chromium(VI) (Fishbein 1981). The wearing down of vehicular brake linings that contain asbestos represents another source of atmospheric chromium. Asbestos may contain ≈1,500 mg/kg of chromium. The introduction of catalytic converters on U.S. automobiles in 1975 in the United States represented an additional source of atmospheric chromium. Catalysts, such as copper chromite, emit <10⁶ metal-containing condensation nuclei per cubic centimeter in vehicular exhaust, under various operating conditions (Fishbein 1981).

Fertilizers also contain chromium and other metals. Commercially available bulk fertilizers had total chromium levels of 50–114 µg/g (Gorman et al. 2011).

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Table 6-4. Chromium Content in Various U.S. Foods

Sample	Mean concentration (µg/kg)	Reference
Fresh vegetables	30–140	EPA 1984a
Frozen vegetables	230	EPA 1984a
Canned vegetables	230	EPA 1984a
Fresh fruits	90–190	EPA 1984a
Fruits	20	EPA 1984a
Canned fruits	510	EPA 1984a
Dairy products	100	EPA 1984a
Chicken eggs	60	Kirpatrick and Coffin 1975
Chicken eggs	160	Schroeder et al. 1962
Chicken eggs	520	Gormican 1970
Whole fish	50–80	EPA 1984a
Edible portion of fresh fin fish	<100–160	Eisenberg and Topping 1986
Meat and fish	110–230	EPA 1984a
Seafoods	120–470	EPA 1984a
Grains and cereals	40–220	EPA 1984a
Sugar, refined ^a	<20	WHO 1988

^aValue in Finnish sugar

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. Home-based exposures can occur to the families of occupational workers in what is known as worker-to-family exposures. Home exposures can also occur through proximity to hazardous waste sites (Pellerin and Booker 2000). A study measured the relationships between chromium in household dust and chromium in the urine of Hudson County, New Jersey residents (Pellerin and Booker 2000). Three major producers of chromium(VI) in the form of chromate were active in the area for over 70 years, and produced over 2 million tons of chromium containing slag waste (Pellerin and Booker 2000). Chromium(VI) levels as high as several hundred parts per million were measured in some of the soil samples extracted from the area (Pellerin and Booker 2000). Similarly, residents living in an area of Taiwan with a large number of electroplating industries had elevated blood chromium levels, and a significant correlation between blood chromium levels and soil chromium levels were found (Chiang et al. 2011).

Dermal exposure of the general public to chromium can occur from skin contact with consumer products that contain chromium. Some of the consumer products known to contain chromium are certain wood preservatives, cement, cleaning materials, textiles, and leather tanned with chromium (WHO 1988). Both chromium(III) and chromium(VI) are known to penetrate the skin, although chromium(VI) penetrates to a higher degree (Robson 2003). Elevated levels of chromium were observed in urine and blood of people who have had knee or hip replacements made with chromium containing metal alloys (Price 2011; Sunderman et al. 1989). Levels of chromium in ambient air ($<0.01\text{--}0.03\text{ }\mu\text{g}/\text{m}^3$) (Fishbein 1984; Pellerin and Booker 2000) and tap water ($<1\text{ }\mu\text{g}/\text{L}$) (Pellerin and Booker 2000) have been used to estimate the daily intake of chromium via inhalation ($<0.2\text{--}0.6\text{ }\mu\text{g}$) and tap water ($<4\text{ }\mu\text{g}$). These estimates are based on an air inhalation rate of $20\text{ m}^3/\text{day}$ and a drinking water consumption rate of $2\text{ L}/\text{day}$. The daily chromium intake for the U.S. population from consumption of selected diets (diets with 25 and 43% fat) has been estimated to range from 25 to 224 μg with an average of 76 μg (Kumpulainen et al. 1979). The chromium concentrations in tissues and body fluids of the general population are given in [Table 6-5](#).

Workers in industries that use chromium can be exposed to concentrations of chromium two orders of magnitude higher than exposure to the general population, and workers in some 80 different professions may be exposed to chromium(VI) (Hemminki and Vainio 1984; Pellerin and Booker 2000). Occupational exposure to chromium occurs mainly from chromate production, stainless steel production and welding,

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Table 6-5. Chromium Content in Tissues and Body Fluids of the General Population

Sample	Median or mean	Range	Reference
Serum	0.006 µg/L	0.01–0.17 µg/L	Sunderman et al. 1989
Urine	0.4 µg/L	0.24–1.8 µg/L	Iyengar and Woittiez 1988
Lung	201 µg/kg (wet weight)	28–898 µg/kg (wet weight)	Raithel et al. 1987
Breast milk	0.30 µg/L	0.06–1.56 µg/L	Casey and Hambidge 1984
Hair	0.234 mg/kg	Not available	Takagi et al. 1986
Nail	0.52 mg/kg	No applicable	Takagi et al. 1988

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chromium plating, ferrochrome alloys and chrome pigment production, and working in tanning industries (Ashley et al. 2003). A list of industries that may be sources of chromium exposure is given in [Table 6-6](#). For most occupations, exposure is due to both chromium(III) and chromium(VI) present as soluble and insoluble fractions. However, exceptions include the tanning industry, where exposure is mostly from soluble chromium(III), and the plating industry, where exposure is due to soluble chromium(VI). The typical concentration ranges of airborne chromium(VI) to which workers in these industries were exposed during an average of 5–20 years of employment were: chromate production, 100–500 $\mu\text{g}/\text{m}^3$; stainless steel welding, 50–400 $\mu\text{g}/\text{m}^3$; chromium plating, 5–25 $\mu\text{g}/\text{m}^3$; ferrochrome alloys, 10–140 $\mu\text{g}/\text{m}^3$; and chrome pigment, 60–600 $\mu\text{g}/\text{m}^3$ (Stern 1982). In the tanning industry, except for two bath processes, the typical exposure range due to chromium(III) was 10–50 $\mu\text{g}/\text{m}^3$. A study of chromium(VI) levels in the air of a chrome plating shop measured concentrations of chromium(VI) in the range of 10–30 $\mu\text{g}/\text{m}^3$ for chrome plating shops with local exhaust (Pellerin and Booker 2000). In plating shops without local exhaust, the levels were much higher, up to 120 $\mu\text{g}/\text{m}^3$ (Pellerin and Booker 2000). In an occupational exposure study of chromium in an aircraft construction factory, airborne samples were collected over a 4-hour period; urinary samples were collected at the beginning (Monday), end (Friday), and after the work shift in order to analyze the absorption of chromium during working hours (Gianello et al. 1998). The air sampling results were 0.02–1.5 mg/m^3 , and the urine sampling results were 0.16–7.74 $\mu\text{g}/\text{g}$ creatinine. Compared to the ACGIH and BEI-ACGIH Hygiene Standard of 50 $\mu\text{g}/\text{m}^3$, both sets of results indicated a very low risk of exposure. The National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 304,829 workers in the United States were potentially exposed to chromium(VI) (NIOSH 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey only estimates the number of workers potentially exposed to chemicals in the workplace.

In a survey of workers in pigment factories in England that produced strontium and lead chromate, the concentrations of chromium in the whole blood in exposed workers ranged from 3 to 216 $\mu\text{g}/\text{L}$, compared to a level of <1 $\mu\text{g}/\text{L}$ for the nonoccupationally exposed population (McAughey et al. 1988). The corresponding concentrations in the urine of exposed workers and the unexposed population were 1.8–575 μg chromium/g creatinine and <0.5 μg chromium/g creatinine, respectively (McAughey et al. 1988).

Other investigators have found a higher lung burden for chromium in occupational groups than in unexposed groups. The median concentration of chromium in the lungs of deceased smelter workers in Sweden was 450 $\mu\text{g}/\text{kg}$ (wet weight), compared to a value of 110 $\mu\text{g}/\text{kg}$ (wet weight) for rural controls and 199 $\mu\text{g}/\text{kg}$ (wet weight) for urban controls (Gerhardsson et al. 1988).

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Table 6-6. Industries that May be Sources of Chromium Exposure

Abrasives manufacturers	Laboratory workers
Acetylene purifiers	Leather finishers
Adhesives workers	Linoleum workers
Aircraft sprayers	Lithographers
Alizarin manufacturers	Magnesium treaters
Alloy manufactures	Match manufacturers
Aluminum anodizers	Metal cleaners
Anodizers	Metal workers
Battery manufacturers	Milk preservers
Biologists	Oil drillers
Blueprint manufacturers	Oil purifiers
Boiler scalers	Painters
Candle manufacturers	Palm-oil bleachers
Cement workers	Paper water proofers
Ceramic workers	Pencil manufacturers
Chemical workers	Perfume manufacturers
Chromate workers	Photoengravers
Chromium-alloy workers	Photographers
Chromium-alum workers	Platinum polishers
Chromium platers	Porcelain decorators
Copper etchers	Pottery frosters
Copper-plate strippers	Pottery glazers
Corrosion-inhibitor workers	Printers
Crayon manufacturers	Railroad engineers
Diesel locomotive repairmen	Refractory-brick manufacturers
Drug manufacturers	Rubber manufacturers
Dye manufacturers	Shingle manufacturers
Dyers	Silk-screen manufacturers
Electroplaters	Smokeless-powder manufacturers
Enamel workers	Soap manufacturers
Explosive manufacturers	Sponge bleachers
Fat purifiers	Steel workers
Fireworks manufacturers	Tanners
Flypaper manufacturers	Textile workers
Furniture polishers	Wallpaper printers
Fur processors	Wax workers
Glass-fibre manufacturers	Welders
Glue manufacturers	Wood-preservative workers
Histology technicians	Wood stainers
Jewelers	

Source: IARC 1990

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A study of seasonal workers who manually replant trees in harvested forests in British Columbia, Canada, examined whether there were potentially higher exposures to arsenic, lead, cadmium, chromium, and nickel for workers who used fertilizer relative to tree planters who did not use fertilizer (Gorman et al. 2011). The study concluded that there was no evidence to suggest that tree planters who worked with fertilizer were at an elevated risk of exposure to these metals as compared to those who did not use fertilizer.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes ingest inappropriate materials (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children living in vicinities where there are chromium waste sites nearby may be exposed to chromium to a greater extent than adults through inhalation of chromium particulates and through contact with contaminated soils. One study has shown that the average concentration of chromium in the urine of children at ages five and younger was significantly higher than in adults residing near sites where chromium waste slag was used as fill material (Fagliano et al. 1997), and the soil levels of a hazardous waste disposal site in New Jersey were measured at levels up to 120 $\mu\text{g}/\text{m}^3$ (Pellerin and Booker 2000). The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented and can result in ingestion of chromium present in soil and dust. Soil may affect the bioavailability of contaminants in several ways, most likely by acting as a competitive sink for the contaminants. In the presence of soil, the contaminants will partition between absorption by the gut and sorption onto the soil particles (Sheppard et al. 1995). If the contaminant is

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irreversibly bound to soil particles, then the contaminant is unlikely to be absorbed in the gastrointestinal tract. Hexavalent chromium exists in soils as a relatively soluble anion and may be present in bioavailable form, possibly with enhanced absorption due to the presence of the soil itself. In contrast, chromium(III) present in soil is generally not very soluble or mobile under most environmental conditions and is not readily bioavailable (James et al. 1997). Studies discussing the oral absorption of chromium in rats from a soil surface in which 30% of the chromium was in hexavalent form and 70% was in trivalent form suggested that while absorption in animals is quite low, chromium appeared to be better absorbed from soil than from soluble chromate salts (Witmer et al. 1989, 1991). However, less than half of the administered dose of chromium could be accounted for in this study, and in separate experiments with low dosages administered to the rats, the control animals actually had higher concentrations of chromium than the animals that were administered the oral dose. Children may accidentally ingest chromium picolinate in households whose members use this product as a dietary supplement unless it is well stored and kept away from children. Small amounts of chromium are used in certain consumer products such as toners in copying machines and printers, but childhood exposure from these sources is expected to be low. Children may also be exposed to chromium from parents' clothing or items removed from the workplace if the parents are employed in a setting where occupational exposure is significant (see Section 6.5). Chromium has been detected in breast milk at concentrations of 0.06–1.56 µg/L (Casey and Hambidge 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies on mice have shown that chromium crosses the placenta and can concentrate in fetal tissue (Danielsson et al. 1982; Saxena et al. 1990a).

A study done on the potential exposure of teenagers to airborne chromium from steel dust in the New York City subway system found significantly higher concentrations of chromium than in home and ambient samples. The conclusion from the study was that the increased concentration was most likely due to steel dust present in the subway system as the source of chromium (Chillrud et al. 2004). Chromium levels in the New York City subway system are greater than ambient levels by approximately two orders of magnitude. Chromium levels observed in the study ($\approx 84 \text{ ng/m}^3$) are similar to chronic reference guidelines in both Canada and the United States and were 40–100 times the adult range in the estimated 10^{-5} lifetime cancer risk (Chillrud et al. 2004). The reference values for exposure to chromium range from 2 to 100 ng/m^3 (Wu et al. 2001). The study measured total chromium levels, without separating the species of chromium into chromium(III) and chromium(VI). Previous studies have suggested that airborne chromium generated from steel welding have a significant amount of chromium(VI) present, extending the possibility that there is a possibility for chromium(VI) to be present in the steel dust in the New York City subway system as well (Chillrud et al. 2004; Edme et al. 1997).

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Another study done on the bones of deceased neonatal humans in Poland found that statistically significant differences in chromium concentrations were observed. In addition, a positive correlation between pairs of metals was observed, specifically between the pairing of chromium and lead. (Baranowski et al. 2002). Bones were chosen to examine, since they are a useful reference in regards to heavy metal exposure and accumulation, and are therefore an accurate measure of chronic exposure.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to chromium (see Section 6.5), there are several groups within the general population that have potentially high exposures (higher-than-background levels) to chromium. Persons using chromium picolinate as a dietary supplement will also be exposed to higher levels of chromium than those not ingesting this product (Anderson 1998b). Like many other products used to promote weight loss or speed metabolism, there is also the potential for overuse of this product by some members of the population in order to achieve more dramatic results (Wasser et al. 1997). People may also be exposed to higher levels of chromium if they use tobacco products, since tobacco contains chromium (IARC 1980).

Workers in industries that use chromium are one segment of the population that is especially at high risk to chromium exposure. Many industrial workers are exposed to chromium(VI) levels in air that exceed the accepted occupational exposure limits (Blade et al. 2007). Occupational exposure from chromate production, stainless steel welding, chromium plating, and ferrochrome and chrome pigment production is especially significant since the exposure from these industries is to chromium(VI). Occupational exposure to chromium(III) compounds may not be as great a concern as exposure to chromium(VI) compounds. Among the general population, residents living near chromate production sites may be exposed to higher levels of chromium(VI) in air. Ambient concentrations as high as $2.5 \mu\text{g}/\text{m}^3$ chromium in air were detected in a 1977 sample from Baltimore, Maryland (EPA 1984a). People who live near chromium waste disposal sites and chromium manufacturing and processing plants may be exposed to elevated levels of chromium. The airborne concentrations of chromium(VI) and total chromium in a contaminated site in Hudson County, New Jersey were studied (Falerios et al. 1992). The mean concentrations of both chromium(VI) and total chromium in indoor air of the contaminated site were about three times higher than the mean indoor air concentrations of uncontaminated residential sites in Hudson County. Although the mean concentration of chromium(VI) in outdoor air was much lower than the current occupational exposure limit of $50 \mu\text{g}/\text{m}^3$, levels in 10 of 21 samples at the contaminated site

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exceeded the background urban outdoor chromium(VI) concentration of 4 ng/m³. Similarly, the total chromium concentration in 11 of 21 outdoor air samples from the contaminated site exceeded the outdoor mean concentration of 15 ng/m³ for urban New Jersey. However, recent sampling data from Hudson County, New Jersey have shown that more than two-thirds of previously sampled sites contaminated with chromite ore processing residue did not have statistically significant mean concentrations greater than the background levels (Scott et al. 1997a). These data, as well as the results of a soil dispersion model (Scott et al. 1997b), suggest that heavy vehicular traffic over unpaved soil surfaces containing chromium(VI) are required for high levels of atmospheric chromium(VI) at these sites. Persons using contaminated water for showering and bathing activities may also be exposed via inhalation to potentially high levels of chromium(VI) in airborne aerosols (Finley et al. 1996a). In a field study to simulate daily bathing activity, airborne chromium(VI) concentrations were about 2 orders of magnitude greater than ambient outdoor air concentrations when water concentrations of 5.4 and 11.5 mg/L were used in the shower.

A study was conducted from September to November 1989 to determine the levels of chromium in urine and red blood cells of state employees who worked at a park (with only indirect exposure potential) adjacent to chromium-contaminated sites in Hudson County, New Jersey (Bukowski et al. 1991). The chromium levels in red blood cells and urine of 17 of these employees showed no differences compared to 36 employees who worked at state parks outside Hudson County. The authors concluded that urinary and blood levels of chromium are poor biological markers in gauging low-level environmental exposure to chromium. This study also concluded that chromium levels in blood and urine depended on other confounding variables, such as exercise, past employment in a chromium-exposed occupation, beer drinking, and diabetic status. Other lifestyle (e.g., smoking), dietary, or demographic factors had no measurable effect on blood and urinary chromium. These conclusions are consistent with the results of a study that measured the urinary excretion of chromium following oral ingestion of chromite ore processing residue material for three days (Finley and Paustenbach 1997). These results indicate no statistical difference in mean urinary chromium concentrations in groups of individuals exposed to chromite ore processing residue material versus the control group. High levels of chromium were detected in the urine and hair of individuals living near a chromite ore-processing plant in Mexico (Rosas et al. 1989), which suggests the possibility of using these media as biological markers in gauging long term, high-level environmental exposure to chromium.

Elevated levels of chromium in blood, serum, urine, and other tissues and organs have been observed in patients with cobalt-chromium knee and hip arthroplasts (Coleman et al. 1973; Michel et al. 1987; Sunderman et al. 1989).

The chromium content in cigarette tobacco from the United States has been reported to be 0.24–6.3 mg/kg (IARC 1980), but neither the chemical form nor the amount of chromium in tobacco smoke is known. People who use tobacco products may be exposed to higher-than-normal levels of chromium.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chromium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. As seen in Section 4.2, the relevant physical and chemical properties of chromium and its compounds are known (Hartford 1979; NIOSH 2008; Weast 1985) and prediction of environmental fate and transport of chromium in environmental media is possible. However, the physical or chemical forms and the mode by which chromium(III) compounds are incorporated into biological systems are not well characterized. The determination of the solubilities of hexavalent chromium compounds in relevant body fluids (e.g., the solubility of chromates in lung fluid) may also be helpful.

Production, Import/Export, Use, Release, and Disposal. Knowledge of a chemical's production volume is important because it may indicate environmental contamination and human exposure. If a chemical's production volume is high, there is an increased probability of general population exposure via consumer products and environmental sources, such as air, drinking water, and food. Data concerning the production (Hartford 1979; Papp and Lipin 2001; SRI 1997; USGS 2008b),

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import (USGS 2008b), and use (CMR 1988a, 1988b; EPA 1984a; IARC 1990; Papp and Lipin 2001; USDI 1988a; USGS 2008b) of commercially significant chromium compounds are available. Chromium is not generally used to process foods for human consumption or added to foods other than diet supplements. Thus, consumer exposure to chromium occurs mostly from natural food sources (Bennett 1986; EPA 1984a; Kumpulainen et al. 1979), but this exposure will increase particularly for people who consume acidic food cooked in stainless steel utensils (Anderson 1981; EPA 1984a). Exposure to chromium occurs to a much lesser extent from products such as toners of photocopying machines, some wood treatment chemicals, and through other chromium-containing consumer products (CMR 1988a, 1988b; EPA 1984a; IARC 1990; USDI 1988a).

As seen in [Tables 6-1](#) and [6-2](#), the largest amount of chromium from production and user facilities is disposed of on land or transferred to an off-site location. More detailed site-and medium-specific (e.g., air, water, or soil) release data for chromium that is disposed of off-site are necessary to assess the exposure potential to these compounds from different environmental media and sources. There are EPA guidelines regarding the disposal of chromium wastes and OSHA regulations regarding the levels of chromium in workplaces (EPA 1988a; OSHA 1998a).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2009, became available in May of 2011. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Information is available to permit assessment of the environmental fate and transport of chromium in air (Pacyna and Pacyna 2001; Schroeder et al. 1987; Scott et al. 1997a, 1997b), water (Cary 1982; Comber and Gardner 2003; EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984; WHO 2003) and soil (Ashley et al. 2003; Avudainayagam et al. 2003; Balasoju et al. 2001; Bartlett 1991; Calder 1988; Cary 1982; Jardine et al. 1999; Rifkin et al. 2004). Chromium is primarily removed from the atmosphere by fallout and precipitation. The residence time of chromium in the atmosphere is expected to be <10 days (Nriagu 1979). Most of the chromium in lakes and rivers will ultimately be deposited in the sediments. Chromium in the aquatic phase occurs in the soluble state or as suspended solids adsorbed onto clayish materials, organics, or iron oxides (Cary 1982). Most of the soluble chromium is present as chromium(VI) or as soluble chromium(III) complexes and generally accounts for a small percentage of the total (Cary 1982). Additional data, particularly regarding chromium's nature of speciation, would be useful to fully assess chromium's fate in air. For example, if chromium(III) oxide

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forms some soluble salt in the air due to speciation, its removal by wet deposition will be faster. No data regarding the half-life of chromium in the atmosphere or a measure of its persistence are available. In aquatic media, sediment will be the ultimate sink for chromium, although soluble chromates may persist in water for years (Cary 1982; EPA 1984a). Additional data elucidating the nature of speciation of chromium in water and soil would also be desirable and a direct measurement of the chromium residence time in the atmosphere would be useful.

Bioavailability from Environmental Media. The bioavailability of chromium compounds from contaminated air, water, soil, or plant material in the environment has not been adequately studied. Absorption studies of chromium in humans and animals provide information regarding the extent and rate of inhalation (Cavalleri and Minoia 1985; Kiilunen et al. 1983; Langård et al. 1978) and oral exposure (Anderson 1981, 1986; Anderson et al. 1983; Donaldson and Barreras 1966; Randall and Gibson 1987; Suzuki et al. 1984). A sorption study has measured the amount of chromium(VI) when iron particles are present in the water samples; the conclusion was that soluble chromium(VI) present in the water could sorb on to iron particles present in the acidic environment of the stomach, and thus, be less bioavailable (Parks et al. 2004). These available absorption studies indicate that chromium(VI) compounds are generally more readily absorbed from all routes of exposure than are chromium(III) compounds. This is consistent, in part, with the water solubilities of these compounds (Bragt and van Dura 1983). The bioavailability of both forms is greater from inhalation exposure than from ingestion or dermal exposure. The bioavailability of chromium from soil depends upon several factors (Witmer et al. 1989). Factors that may increase the mobility of chromium in soils include the speculated conversion of chromium(III) to chromium(VI), increases in pH, and the complexation of chromium(III) with organic matter from water-soluble complexes. Data on the bioavailability of chromium compounds from actual environmental media and the difference in bioavailability for different media need further development.

Food Chain Bioaccumulation. It is generally believed that chromium does not bioconcentrate in fish (EPA 1980, 1984a; Fishbein 1981; Schmidt and Andren 1984) and there is no indication of biomagnification of chromium along the aquatic food chain (Cary 1982). However, recent skin biopsy data indicate that North Atlantic right whales are exposed to hexavalent chromium and accumulate a range of 4.9–10 µg chromium/g tissue with a mean of 7.1 µg chromium/g tissue (Wise et al. 2008). Some data indicate that chromium has a low mobility for translocation from roots to aboveground parts of plants (Cary 1982; WHO 1988). However, more data regarding the transfer ratio of chromium from soil to plants and biomagnification in terrestrial food chains would be desirable.

Exposure Levels in Environmental Media. The atmospheric total chromium concentration in the United States is typically $<10 \text{ ng/m}^3$ in rural areas and $10\text{--}30 \text{ ng/m}^3$ in urban areas (Fishbein 1984; WHO 2003). Most drinking water supplies in the United States contain $<5 \text{ }\mu\text{g/L}$ of chromium (WHO 2003). The chromium level in soils varies greatly and depends on the composition of the parent rock from which the soils were formed. Basalt and serpentine soils, ultramafic rocks, and phosphorites may contain chromium as high as a few thousand mg/kg (Merian 1984), whereas soils derived from granite or sandstone will have lower concentrations of chromium (Swaine and Mitchell 1960). The concentration range of chromium in 1,319 samples of soils and other surficial materials collected in the conterminous United States was $1\text{--}2,000 \text{ mg/kg}$, with a geometric mean of 37 mg/kg (USGS 1984). There is a large variation in the available data regarding the levels of chromium in foods (EPA 1984a). Concentrations ranges are $30\text{--}230 \text{ }\mu\text{g/kg}$ in vegetables, $20\text{--}510 \text{ }\mu\text{g/kg}$ in fruits, $40\text{--}220 \text{ }\mu\text{g/kg}$ in grains and cereals, and $110\text{--}230 \text{ }\mu\text{g/kg}$ in meats and fish (EPA 1984a). It would be useful to develop nationwide monitoring data on the levels of chromium in U.S. ambient air and drinking water, and these data should quantitate levels of both chromium(III) and chromium(VI) and not just total chromium. EPA is working with state and local officials to determine the prevalence of chromium (VI) in drinking water (Erickson 2011; Kemsley 2011).

Exposure Levels in Humans. The general population is exposed to chromium by inhaling ambient air and ingesting food and drinking water containing chromium. Dermal exposure of the general public to chromium can occur from skin contact with certain consumer products that contain chromium or from contact with chromium contaminated soils. Some of the consumer products known to contain chromium are certain wood preservatives, cement, cleaning materials, textiles, and leather tanned with chromium (WHO 1988). However, no quantitative data for dermal exposure to chromium-containing consumer products were located. Levels of chromium in ambient air ($<0.01\text{--}0.03 \text{ }\mu\text{g/m}^3$) (Fishbein 1984; WHO 2003) and tap water ($<2 \text{ }\mu\text{g/L}$) (WHO 2003) have been used to estimate the daily intake of chromium via inhalation ($<0.2\text{--}0.6 \text{ }\mu\text{g}$) and tap water ($<4 \text{ }\mu\text{g}$). These estimates are based on an air inhalation rate of $20 \text{ m}^3/\text{day}$ and a drinking water consumption rate of 2 L/day . The daily chromium intake for the U.S. population from consumption of selected diets (diets with 25 and 43% fat) has been estimated to range from 25 to $224 \text{ }\mu\text{g}$, with an average of $76 \text{ }\mu\text{g}$ (Kumpulainen et al. 1979). This value is within the range established by the World Health Organization (WHO) as a mean chromium intake from food and water of $52\text{--}943 \text{ }\mu\text{g/day}$ (WHO 2003). However, few data on the levels of chromium in body tissues or fluids for populations living near hazardous waste sites are available. Such data could be a useful tool as an early warning system against harmful exposures. In addition, there is a need for data on the background levels

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of chromium in body fluids of children. Such data would be important in assessing the exposure levels of this group of people.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Limited data exist regarding exposure and body burdens of chromium in children. Chromium has been detected in breast milk at concentrations of 0.06–1.56 µg/L (Casey and Hambidge 1984), suggesting that children could be exposed to chromium from breast-feeding mothers. Studies in mice have shown that chromium crosses the placenta and can concentrate in fetal tissue (Danielsson et al. 1982; Saxena et al. 1990a). Because children living near areas contaminated with chromium have been shown to have elevated chromium levels in urine as compared to adults (Fagliano et al. 1997), additional body burden studies are required to evaluate the exposures and the potential consequences that this might have upon children. This is particularly important around heavily contaminated soils where children may be exposed dermally or through inhalation of soil particulates during play activities. These studies may determine if children may be more susceptible than adults to the toxic effects of chromium including immunosensitivity. Studies are necessary that examine children's weight-adjusted intake of chromium and determine how it compares to that of adults. Since chromium is often detected in soil surfaces and children ingest soil either intentionally through pica or unintentionally through hand-to-mouth activity, pica is a unique exposure pathway for children. Studies have shown that although absorption of chromium is low, it may be enhanced slightly from contaminated soil surfaces (Witmer et al. 1989, 1991).

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for chromium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1 (see [Table 6-7](#)).

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Table 6-7. Ongoing Studies on Chromium

Principal investigator	Affiliation	Research description
David Brautigan	University of Virginia	Define the biochemical basis of chromium enhancement of insulin action
William Cefalu	Pennington Biomedical Research Center	Study the changes in insulin uptake on chromium supplementation
Mitchell Cohen	New York University School of Medicine	Study biological interactions of metals and improve design of metallopharmaceuticals
Jeffrey Elmendorf	Indiana University: Purdue University at Indianapolis	Chromium action and role in the glucose transport system
Emily Horvath	Indiana University: Purdue University at Indianapolis	Cellular insulin resistance mechanisms
Joshua Jacobs	Rush University Medical Center	Metal release and effects in people with metal-on-hip replacements
Sushil Jain	Louisiana State University	Cytokine production; role of chromium in preventing oxidative stress
Umesh Masharani	University of California, San Francisco	The effects of chromium on insulin action
Mahmood Mozaffari	Medical College of Georgia	Effect of chromium on glucose metabolism
Charles Myers	Medical College of Wisconsin	Study the mechanisms of chromium(VI) in the human lung system
Patricia Opresko	University of Pittsburgh at Pittsburgh	Understand the mechanisms of genomic instability associated with aging
Viresh Rawal	University of Chicago	Investigation of metal-salen complexes for use in C-C bond forming reactions; Diels-Alder catalyst development
James Rigby	Wayne State University	Study metal mediated cyclo-addition reactions to synthesize natural products
Diane Stearns	Northern Arizona University	Study the difference in mutations caused by soluble chromium vs. insoluble chromium; discover mechanism of cellular entry by soluble chromium compounds
Kent Sugden	University of Montana	Study the role of chromium in DNA mutations and cancer
Bo Xu	Southern Research Institute	The effect of chromium exposure on DNA damage
Ziling Xue	University of Tennessee, Knoxville	Development of an analytical method to determine chromium levels in biological fluids
Anatoly Zhitkovich	Brown University	Study the role of chromium in genetic alteration of cells after exposure

Source: FEDRIP 2008

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring chromium compounds, their metabolites, and other biomarkers of exposure to chromium compounds. The intent is not to provide an exhaustive list of analytical methods, but to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to lower detection limits and/or to improve accuracy and precision in detection.

7.1 BIOLOGICAL MATERIALS

Several methods are available for the analysis of chromium in different biological media, with some methods of chromium determination summarized in [Table 7-1](#). Multiple reviews on the subject provide more detailed descriptions of the available analytical methods (EPA 1984a; Fishbein 1984; IARC 1986a, 1990; Torgrimsen 1982; WHO 1988). Frequently used techniques for determining low levels of chromium in biological samples include neutron activation analysis (NAA) (Cornelis 1985; Greenberg and Zeisler 1988); inductively-coupled plasma-mass spectrometry (ICP-MS) (Bonnefoy et al. 2005; D'illio et al. 2011; McShane et al. 2007); graphite furnace atomic absorption spectrometry (GFAAS) (Dube 1988; Randall and Gibson 1987)); and electrothermal atomization-atomic absorption spectrometry (ET-AAS) (Olmedo et al. 2010).

There are numerous issues and considerations in collecting and analyzing the chromium content in presented samples. Some of these issues include problems with collection, contamination, and determining accurate concentration levels of the chromium content in the samples. The determination of trace quantities of chromium in biological materials requires special precautionary measures, from the initial sample collection process to the final analytical manipulations of the samples. The sample collection and handling of human blood and urine samples as it pertains to the analysis of trace metals including chromium has been discussed elsewhere (Cornelis et al. 1996). For chromium, a stainless steel needle should not be used for blood collection due to possible contamination of the sample, and it is advised that any anti-coagulants used be analyzed for the presence of chromium. In addition, acid-

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Table 7-1. Analytical Methods for Determining Chromium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma	Wet ashing with $\text{HNO}_3/\text{HClO}_4/\text{H}_2\text{SO}_4$; residue complexed with APDC and extracted with MIBK; evaporated residue dissolved deposited in HNO_3/HCE , and solution on a polycarbonate foil	PIXE	0.3 $\mu\text{g/L}$	87% at 4.5 $\mu\text{g/g}$	Simonoff et al. 1984
Blood, serum	Sample after wet digestion converted to a volatile chelate usually with fluorinated acetylacetone	GC/ECD	0.03 pg 0.5 pg 1.0 ng	No data	Fishbein 1984
Serum	$\text{Mg}(\text{NO}_3)_3$ added to serum, dried by Lyophilization, ashed, and dissolved in 0.1 N HCl	GFAAS	0.005 $\mu\text{g/L}$	103% at 0.30 $\mu\text{g/L}$	Randall and Gibson 1987
Blood	Diluted with 0.1% EDTA and 5% isopropanol	GFAAS-Zeeman-effect background correction	0.09 $\mu\text{g/L}$	No data	Dube 1988
Blood	Collect blood samples in glass tubes containing sodium heparinate to prevent coagulation and store at 4 °C	ICP-MS	2.5 $\mu\text{g/L}$	No data	Bonnefoy et al. 2005
Blood	Collection and storage at 4 °C	ET-AAS	0.19 $\mu\text{g/L}$	99.15%	Olmedo et al. 2010
Blood or tissue	Wet ashing with $\text{HNO}_3/\text{HClO}_4/\text{H}_2\text{SO}_4$	ICP-AES	1 $\mu\text{g}/100\text{ g}$ blood 0.2 $\mu\text{g/g}$ tissue	114% recovery at 10 $\mu\text{g/sample}$	NIOSH 1994a (Method No. 8005)
Erythrocytes	Dilution with Triton X100	GFAAS	No data	No data	Lewalter et al. 1985
Serum and urine	HNO_3 de-proteinization	ET-AAS	0.02 $\mu\text{g/L}$ (serum) 0.1 $\mu\text{g/L}$ (urine)	No data	Sunderman et al. 1989

Table 7-1. Analytical Methods for Determining Chromium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Body fluids (milk, urine, etc.)	Dried sample ashed by oxygen plasma, H ₂ O ₂ addition, drying, dilution in 1N HCl	GFAAS with tungsten iodide or deuterium arc or CEWM background correction	<0.25 µg/L	91% at 0.55 µg/L	Kumpulainen 1984
Urine	None	GFAAS	0.05 µg/L	91% at 0.22 µg/L	Randall and Gibson 1987
Urine	None	GFAAS with CEWM background correction and WM-AES	0.09 µg/L (CEWM-AAS) 0.02 µg/L (WM-AES)	No data	Harnly et al. 1983
Urine	No sample preparation other than addition of yttrium internal standard	ICP-AES	12 µg/L	77% at 13 µg/L	Kimberly and Paschal 1985
Urine	Sorption onto polydithiocarbonate resin, ash sorbate in low temperature oxygen plasma and dissolve in HNO ₃ /HClO ₄	ICP-AES	0.1 µg/sample	100% recovery at 1 µg/50mL urine	NIOSH 1994b (Method 8310)
Urine	None	GFAAS	0.0052 µg/L	No data	Kiilunen et al. 1987
Urine	Sample spiked with standard chromium (standard addition)	GFAAS	0.03–0.04 µg/L	No data	Veillon et al. 1982
Urine	Diluted with water	GFAAS-Zeeman-effect-background correction	0.09 µg/kg	No data	Dube 1988
Urine	Samples collected and diluted for analysis with 2% (v/v) double-distilled grade ultrapure nitric acid (and 0.002% Triton X-100 (diluent)	ICP-MS	0.26 µg/L	No data	McShane et al. 2007
Urine	Collection and storage at 4 °C with or without dilute nitric acid solution.	ET-AAS	0.19 µg/L	101.74%	Olmedo et al. 2010
Milk powder	Mixed with water	GFAAS	5 µg/kg	134–141% at 17.7 µg/kg	Wagley et al. 1989

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Table 7-1. Analytical Methods for Determining Chromium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissue(Chromium(V))	Injection of sodium dichromate	EPR	0.1 mmol/kg	No data	Liu et al. 1994
Hair	Wash with double-distilled water and neutral soap followed by acid digestion	ETAAS	0.19 µg/L	103.00%	Olmedo et al. 2010

AAS = atomic absorption spectrometry; APDC = ammonium pyrrolidine dithiocarbonate; CEWM = continuum source echelle monochromator wavelength-modulated; ECD = electron capture detector; EDTA = ethylenediaminetetraacetic acid; EPR = electron paramagnetic resonance spectroscopy; ET-AAS = electrothermal-atomic absorption spectrometry GC = gas chromatography; GFAS = graphite furnace AAS; H₂O₂ = hydrogen peroxide; H₂SO₄ = sulfuric acid; HCl = hydrochloric acid; HClO₄ = perchloric acid; HNO₃ = nitric acid; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; Mg(NO₃)₃ = magnesium nitrate; MIBK = methylisobutyl ketone; MS = mass spectrometry; PIXE = proton-induced X-ray emission spectrometry; XRF = X-ray fluorescence analysis; WM-AES = wavelength-modulated atomic emission spectrometry

washed plastic tubes are required for blood collection. Unwashed commercially available tubes were found to contain trace amounts of chromium in blank samples (Cornelis et al. 1996).

Contaminates including dust contamination or losses of the samples during collection, transportation, and storage should be avoided (EPA 1984a). Chromium-containing grinding and homogenizing equipment should not be used for preparation of biological samples. Reagents of the highest purity should be used to avoid contamination, and the potential loss of chromium due to volatilization during wet and dry ashing should be minimized (EPA 1984a).

The determination of chromium in most biological samples is difficult because of the matrix interference and the very low concentrations present in these samples. Prior to 1978, numerous erroneous results were reported for the chromium level in urine using electrothermal atomic absorption spectrometry (EAAS) because of the inability of conventional atomic absorption spectrometry systems to correct for the high nonspecific background absorption. Similarly, the reported serum and plasma chromium concentrations of normal subjects have varied more than 5,000-fold since the early 1950s. A limitation of ICP-MS is the presence of other elements that may combine with plasma argon ions to form polyatomic ions. The main polyatomic ions that interfere with the analysis of chromium are $^{40}\text{Ar}^{12}\text{C}^+$, $^{36}\text{Ar}^{16}\text{O}^+$, $^{38}\text{Ar}^{14}\text{N}^+$, $^{35}\text{Cl}^{16}\text{O}^+\text{H}^+$, and $^{37}\text{Cl}^{15}\text{O}^+$ because they have similar mass-to-charge ratios as the most abundant isotope of chromium, $^{52}\text{Cr}^+$ (D'illio et al. 2011). Matrix interference problems have been improved by using ICP-MS equipped with a dynamic reaction cell (DRC) (Bonney et al. 2005; D'illio et al. 2011; McShane et al. 2007). The DRC contains a gas such as ammonia, which can react with polyatomic ions such as $^{40}\text{Ar}^{12}\text{C}^+$ resulting in a new species with a different mass-to-charge ratio.

The chromium levels in human serum or plasma as reported in the mid-1980s ranged from 0.01 to 0.3 $\mu\text{g/L}$ (Anderson 1987) and the daily urinary excretion rate of chromium in healthy and nonoccupationally exposed humans range from approximately 0.24 to 1.8 $\mu\text{g/L}$; however, these levels are greatly influenced by food and beverage intake, smoking, and exercise (Paustenbach et al. 1997).

The problem with generating accurate data for chromium in biological materials in the past was associated with the lack of Standard Reference Materials (SRM). Recently, the National Institute of Standards and Technology (NIST) with collaboration of Centers for Disease Control and Prevention (CDC) released a new reference material (SRM 2668), toxic elements in frozen human urine, which contains chromium among other elements (DOC 2012). This will significantly improve the precision and accuracy of the analytical measurements of chromium in clinical samples. However, due to the previous

lack of SRMs, older data should be interpreted with caution (EPA 1984a), unless the data are verified by interlaboratory studies (WHO 1988).

In addition to the consideration of contamination and potential loss of sample, it should be noted that chromium may exist as several different oxidation states in biological media. Two of the most common oxidation states are chromium(III) and chromium(VI). Each of these oxidation states displays very different physical and biological properties. In biological samples where chromium is generally present as chromium(III), the choice of a particular method is dictated by several factors, including the type of sample, its chromium level, and the scope of the analysis (Kumpulainen 1984).

7.2 ENVIRONMENTAL SAMPLES

Analytical methods for determining chromium in environmental samples are reported in [Table 7-2](#). Many of the issues that affect the measurement of chromium in biological samples are also present in environmental analysis, including issues of collection, contamination, and detection. Chromium may be present in both the trivalent and hexavalent oxidation states in most ambient environmental and occupational samples, as well as existing in soluble and insoluble forms. Soluble chromium(VI) may be reduced to chromium(III) on some filtering media, particularly at low concentrations, and under acidic conditions. Teflon[®] filter and alkaline solution are most suitable to prevent this reduction (Sawatari 1986). As in the case of biological samples, contamination and chromium loss in environmental samples during sample collection, storage, and pretreatment should be avoided. Chromium loss from aqueous samples due to adsorption on storage containers should be avoided by using polyethylene or similar containers and adjusting the solution to the proper pH.

Methods are available for the detection of hexavalent chromium in airborne particulate matter based on ion chromatography followed by UV-VIS spectroscopy (Ashley et al. 2003; ASTM 2008 [Method D6832]; CARB 1990; ISO 2005 [Method 16740]; NIOSH 2003a [Method 7605]; Sheehan et al. 1992). In general, a known volume of air is drawn through a filter to collect particulate chromium in workplace air and these samples are dissolved to extract hexavalent chromium. Following dissolution and treatment with ion chromatography in order to separate the extracted hexavalent chromium from trivalent chromium and other metal cations, the solutions are derivitized with 1,5-diphenylcarbazide to form a chromium diphenylcarbazone complex, which has a characteristic absorption band at approximately 540 nm. Field-portable instruments that can be employed to rapidly measure chromium(VI) levels in workplace air have been developed based upon these methods (NIOSH 2003b [Method 7703]; Wang et al. 1999). Different

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Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (total chromium)	Air particulate matter collected on filter is cut out and irradiated with X-ray photons	XRF	0.017 µg/m ³	No data	Wiersema et al. 1984
Air (total chromium)	The collected particulates in filter dissolved in HNO ₃ , dried and redissolved in acidified water	ICP-AES	0.05–0.2 ng/m ³	No data	Barrie and Hoff 1985
Air (total chromium)	Particulate matter collected on cellulose ester filter, digested with aqua regia	ICP-AES	1 µg/m ³	87–102% at 0.5–100 µg	Lo and Arai 1988
Air (total chromium)	Air particulate collected on cellulose ester filter, wet wash with HCl/HNO ₃	Flame atomic absorption	0.06 µg/sample	98% at 45–90 µg/sample	NIOSH 1994c (Method 7024)
Air (total chromium)	Sample collected on cellulose ester membrane filter dissolved in acid mixtures	ICP-AES	1 µg/sample	98% at 2.5 µg/filter	NIOSH 1994d (Method 7300)
Air (total chromium)	Collect 80 m ³ air using polystyrene filters	NAA	0.25 ng/m ³	No data	Schroeder et al. 1987
Air (chromium(VI))	Sample collected on sodium carbonate-impregnated cellulose filter and extracted with sodium bicarbonate followed by separation and derivatization with diphenylcarbazide solution	Ion chromatography with post-column derivatization and UV-VIS detection	0.1 ng/m ³ for 20 m ³ sample	89–99% at 100 ng	CARB 1990
Air (chromium(VI))	Sample collected on sodium carbonate-impregnated cellulose filter and extracted with sodium bicarbonate followed by separation and derivatization with diphenylcarbazide solution	Ion chromatography with post-column derivatization and UV-VIS detection	0.1 ng/m ³ for 20 m ³ sample	87–101 % (94% mean)	Sheehan et al. 1992

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (chromium(VI))	Sample collected on PVC filter followed by extraction, separation and derivatization with diphenylcarbazide solution	Ion chromatography with post-column derivatization and UV-VIS detection	0.25 $\mu\text{g}/\text{m}^3$ for 200 L samples	94.8%	NIOSH 2003a (Method 7605)
Occupational air (chromium VI)	A known volume of air is drawn through a filter to collect particulate hexavalent chromium and then dissolved; following separation, derivatization with diphenylcarbazide solution	Ion chromatography with post-column derivatization and UV-VIS detection	0.1–100 $\mu\text{g}/\text{m}^3$ for 1 m^3 air	96%	ASTM 2008 (Method D6832)
Occupational air (chromium VI)	A known volume of air is drawn through a filter to collect particulate hexavalent chromium and then dissolved; following separation, derivatization with diphenylcarbazide solution	Ion chromatography with post-column derivatization and UV-VIS detection	0.01–10 $\mu\text{g}/\text{m}^3$ for 1 m^3 air	96%	ISO 2005 (Method 16740)
Occupational air (welding fumes)	Particulate matter captured on the filter was dissolved with hot H_2SO_4 and chromium(III) was oxidized to chromium(VI) by addition of Na_2O_2 ; iron and other metals that form insoluble hydroxides were removed by centrifugation; the centrifuged solution was acidified with HCl and reduced to chromium(III) by SO_2 ; the solution was complexed with β -isopropyl tropolone in CHCl_3	HPLC-UV	10 pg	No data	Maiti and Desai 1986
Occupational air (chromium (VI))	Extract with 0.05 M $(\text{NH}_4)_2\text{SO}_4$ –0.5 M $(\text{NH}_4)_2\text{SO}_4$. 1 M NH_3 .	FIA-UV/VIS	0.11 ng	>90%	Wang et al. 1997a

7. ANALYTICAL METHODS

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Simultaneous determination of chromium(III) and chromium(VI) in water extract from metal fumes	Sample solution at pH 5 reacted with disodium ethylenediamine tetraacetic acid at 50 °C for 1 hour	HPLC on anion exchange column with Na ₂ CO ₃ eluting solution and simultaneous UV and AAS detection	0.2 ng by UV for chromium(VI) 2.0 ng by UV 5.0 ng by AAS for chromium (IV) 5 ng by AAS for chromium (III)	95–105% at 0.002–2.0 µg	Suzuki and Serita 1985
Atmospheric deposition (snow)	The melted snow filtered through Nucleopore filter; the filtrate acidified with HNO ₃ ; and dried by freeze-drier; residue dissolved in HNO ₃ ; this preconcentrated solution placed in plastic tubes; both plastic tube and Nucleopore filter irradiated with protons	PIXE	2 µg/L (soluble portion) 26 µg/L (snow particle)	No data	Jervis et al. 1983; Landsberger et al. 1983
	Either the above Nucleopore filter or the preconcentrated liquid placed in plastic vial is irradiated by thermal neutron	NAA	5 µg/L (soluble portion) 115 µg/g (snow particle)	No data	Jervis et al. 1983; Landsberger et al. 1983
Drinking water (dissolved chromium(VI))	The sample is introduced directly into the ion chromatograph and Cr(VI) is separated from the other matrix components by an anion exchange column followed by derivatization with diphenylcarbazide	Ion chromatography with post-column derivatization and UV-VIS detection	0.0044–0.015 µg/L	87.1–103% (results for different types of water and preservatives used)	EPA 2011 (Method 218.7)
Drinking water, surface water, and certain domestic and industrial effluents (dissolved chromium(VI))	Complex chromium(VI) in water with APDC at pH 2.4 and extracted with MIBK	AAS	2.3 µg/L	No data	EPA 1983b (Method 218.4)

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, groundwater and water effluents (chromium(VI))	Buffer solution introduced into ion chromatograph. Derivatized with diphenylcarbazide	Ion chromatography with post-column derivatization and UV-VIS detection	0.3 µg/L	100% at 100 µg/L	EPA 1996a (Method 7199)
Waste water and industrial effluent for chromium(VI) only	Buffered sample mixed with AlCl ₃ and the precipitate separated by centrifugation or filtration	DPPA at pH 10–12	30 µg/L	90% at 0.2 mg/L	Harzdorf and Janser 1984
Waste water 1986 (chromium(VI))	Derivatization with o-nitrophenylfluorone	UV-VIS spectrometry at 582 nm	Lower than diphenylcarbazone method	No data	Qi and Zhu 1986
Water (total chromium)	Calcium nitrate added to water and chromium is converted to chromium(III) by acidified H ₂ O ₂	GFAAS or ICP/AES	1.0 µg/L (GFAAS) 7.0 µg/L	97–101% at 19–77 µg/L	EPA 1983a, 1986a (Method 218.2 and 7191)
Water (chromium(III) and chromium(VI))	Solid-phase extraction using anion exchange resins for Cr(VI) adsorption and chelating resins for Cr(III) adsorption	ICP-MS	0.009 µg/L (chromium VI); 0.03 µg/L (chromium III)	86–113%	Guerrero et al. 2012
Seawater (total chromium)	Derivatization with trifluoroacetylacetone and solid-phase microextraction	ICP-MS	9.1–20 pg/L	No data	Yang et al. 2004
Industrial wastes, soils, sludges, sediments, and other solid wastes (total chromium)	Digest with nitric acid/hydrogen peroxide	ICP-AES	4.7 µg/L	101% at 3.75 mg/L	EPA 1996b (Method 6010b)
Oil wastes, oils, greases, waxes, crude oil (soluble chromium)	Dissolve in xylene or methyl isobutyl ketone	AAS or GFAAS	0.05 mg/L	107% at 15 µg/L	EPA 1986b (Method 7190)

7. ANALYTICAL METHODS

Table 7-2. Analytical Methods for Determining Chromium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, domestic and industrial waste (chromium[VI])	Chromium(VI) is coprecipitated with lead sulfate, reduced, and resolubilized in nitric acid	AAS or GFAAS	0.05 mg/L (AAS) 2.3 µg/L (GFAAS)	93–96% at 40 µg/L	EPA 1986c (Method 7195)
Groundwater-EP extract, domestic, and industrial waste (chromium[VI])	Chelation with ammonium pyrrolidine dithiocarbamate and extraction with methyl isobutyl ketone	AAS	No data	96% at 50 µg/L	EPA 1983b, 1986d (Method 218.4 and 7197)
Water, waste water, and EP extracts (chromium(VI))	Direct	DPPA	10 µg/L	93% at 5 mg/L	EPA 1986e (Method 7198)
Soil, sediment and sludges (chromium(VI))	Acid digestion extraction using hot HNO ₃	GFAAS	No data	No data	Oygard et al. 2004
Sediment (total chromium)	Samples digested with HNO ₃ and HF and dried	XRF	No data	No data	Adekola and Eletta (2007)
Sediment	Acid digestion using 0.5N HCl followed by filtration	AAS	No data	94.88%	Ayyamperumal 2006

AAS = atomic absorption spectrophotometry; AlCl₃ = aluminum chloride; APDC = ammonium pyrrolidine dithiocarbamate; CHCl₃ = chloroform; DPPA = differential pulse polarographic analysis; EAAS = electrothermal atomic absorption spectrometry; EP = extraction procedure (for toxicity testing); FIA/uv/vis = flow injection analysis-ultraviolet/visible spectroscopy; GFAAS = graphite furnace atomic absorption spectrometry; H₂SO₄ = sulfuric acid; HCl = hydrochloric acid; HF = hydrofluoric acid; HNO₃ = nitric acid; HPLC = high pressure liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectrometry; NAA = neutron activation analysis; MIBK = methylisobutyl ketone; Na₂O₂ = sodium peroxide; NaOH = sodium hydroxide; Na₂CO₃ = sodium carbonate; (NH₄)₂SO₄ = ammonium sulfate; NH₃ = ammonia; PIXE = proton-induced X-ray emission spectrometry; SO₂ = sulfur dioxide; UV = ultraviolet; XRF = X-ray fluorescence analysis

procedures may be employed for the extraction of soluble versus insoluble hexavalent chromium compounds and the various sequential extraction procedures described in standardized methods ASTM D6832 and ISO 16740 have been compared for their effectiveness for recovering hexavalent chromium from workplace air (Ashley et al. 2009). A three-step sequential extraction procedure was outlined that employed deionized water to dissolve soluble chromium compounds such as potassium chromate, an ammonium sulfate buffer for sparingly soluble species, and a sodium carbonate buffer to dissolve insoluble chromium complexes such as lead chromate. Recovery data for chromium compounds spiked onto PVC filters suggested that the three-step procedure may result in excessively high recoveries of soluble chromium species. A two-step extraction process using either water or sulfate buffer to dissolve soluble hexavalent chromium compounds followed by sonication in a carbonate buffer to obtain insoluble species yielded acceptable results when applied to the analysis of hexavalent chromium in paint pigments and stainless steel welding fumes (Ashley et al. 2009).

Measurements of low levels of chromium concentrations in water have been made by methods, such as ICP-MS (Guerrero et al. 2012; Henshaw et al. 1989; Parks et al. 2004; Yang et al. 2004), GFAAS (Gonzalez et al. 2005), ICP-AES (Malinski et al. 1988), and high resolution capillary column gas chromatography (HRGC) with ECD (Schaller and Neeb 1987). EPA Method 218.7 uses ion chromatography followed by derivatization with 1,5-diphenylcarbazide and UV-VIS analysis for the detection of hexavalent chromium in drinking water (EPA 2011). Proper storage and maintenance of water samples is critical since chromium(III) can be oxidized to chromium(VI) especially in the presence of free chlorine. Samples are typically stored at pH 8 or above and with buffers containing ammonium ions to complex free chlorine. Methods using high performance liquid chromatography (HPLC) interfaced with a direct current plasma emission spectrometer have also been used for the determination of chromium(III) and chromium(VI) in water samples (Krull et al. 1983). Abranko et al. (2004) employed GC-ECD, electron impact-mass spectrometry (EI-MS) and ICP-MS to the quantification of chromium in seawater following derivatization with trifluoroacetylacetone and solid phase microextraction (SPME). Detection limits ranging from 0.011 to 0.015 ng/mL were reported for all three techniques. Acid leachable and digestion procedures followed by AAS have been developed that can quantify chromium(VI) and total chromium in soil, sediment, and sludge (Ayyamperumal 2006; Oygard et al. 2004). The preferred methods for digestion of environmental samples have been discussed by Griepink and Tolg (1989) and Parks et al. (2004).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chromium compounds is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chromium compounds.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. There are studies correlating chromium in urine (Cocker et al. 2007; Gylseth et al. 1977; Kilburn et al. 1990; Lindberg and Vesterberg 1983a; McAughey et al. 1988; Minoia and Cavalleri 1988; Mutti et al. 1985b; Sjogren et al. 1983; Tola et al. 1977), blood (Kilburn et al. 1990; Lewalter et al. 1985; McAughey et al. 1988; Wiegand et al. 1988), hair (Randall and Gibson 1987, 1989; Takagi et al. 1986), hair in children (Chiba et al. 2004), nails (Takagi et al. 1988), and erythrocytes (Lukanova et al. 1996) to occupational exposure levels. Since chromium is an essential element, levels of chromium compounds have to be relatively high in humans before they signify an increase due to exposure. Hair has been useful in determining chronic occupational exposure to chromium in high concentrations (Randall and Gibson 1989), although the utility of this method for detecting prior exposures has a limited timespan of months (Simpson and Gibson 1992). Analytical methods to detect chromium concentrations in urine (Randall and Gibson 1987), whole blood (Case et al. 2001; Dube 1988; Fahrni 2007), serum/plasma (Simonoff et al. 1984), and tissue (Fahrni 2007; Liu et al. 1994) have been reported. Generally, the detection limits are in the sub ppb to ppb range, and recoveries are good (>70%).

Chromium induced DNA-protein complexes were prepared as a biomarker of exposure, as discussed in Section 3.12.2. These complexes can be detected by potassium chloride-sodium dodecyl sulfate mediated precipitation. These methods have a number of inherent limitations including tedious methodology and

being subject to considerable interindividual and interlaboratory variations (Singh et al. 1998b). Only one study has attempted to utilize this biomarker, and it was found that volunteers exposed to chromium in drinking water showed no increase in protein-DNA crosslinking in blood cells (Kuykendall et al. 1996). This suggests that this procedure may not be sensitive enough for use in environmental monitoring unless an individual has received a potentially toxic level of exposure. In addition, chromium forms chromium-DNA complexes inside of cells, and these complexes constitute a potential biomarker for the assessment of environmental or occupational exposure. A novel method has been described for the sensitive detection of chromium-DNA adducts using inductively coupled plasma mass spectrometry (Singh et al. 1998b). The detection limits of this method are in the parts per trillion range and allow for the detection of as few as 2 chromium adducts per 10,000 bases, which coupled with the low DNA sample requirements, make this method sensitive enough to measure background levels in the population. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children.

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Methods are available and in use for detecting chromium in air, water, and soil environments. Methods have been developed that can determine low levels of total chromium and chromium(VI) in the air, with detection limits in the ng/m³ range and excellent recoveries (90% or better) (Ashley et al. 2003; Barrie and Hoff 1985; CARB 1990; NIOSH 2003a; Sheehan et al. 1992). These methods are sufficient to determine background chromium levels in the environment and levels at which health effects may occur. There are also field-portable instruments that can be employed to rapidly measure chromium(VI) levels in workplace air (NIOSH 2003b; Wang et al. 1999). Chromium can be detected in water at concentrations in the ppb range (Abu-Saba and Flegal 1997; EPA 1983a, 1996a; Harzdorf and Janser 1984 Parks et al. 2004) and household and bottled drinking water (Al-Saleh and Al-Doush 1998), with recoveries of ≥90% being reported in some studies. In addition, there are also methods that can differentiate chromium(VI) from chromium(III) in water samples (EPA 1986c, 2011). A reliable analytical method for extracting and quantifying chromium from soil surfaces has also been reported (Ayyamperumal et al. 2006; Oygard et al. 2004). Analytical methods exist that are sufficient for measuring background levels of chromium in soil (Ayyamperumal et al. 2006; EPA 1996b; Finley and Paustenbach 1997; Oygard et al. 2004) and water (EPA 1983a, 1983b, 1983c, 1986a, 1996a; Finley and Paustenbach 1997) and also water samples collected from various geological sites of interest (Gonzalez et al. 2005; Parks et al. 2004).

7.3.2 Ongoing Studies

Analytical methods for the detection of chromium compounds at increasingly lower concentrations are currently under development. Targeted areas of interest include air, water, and soil monitoring, with special emphasis being placed on populations considered vulnerable or potentially at risk, such as children and occupational workers. Additionally, more reliable methods to separate chromium(III) analysis from chromium(VI) analysis in collected samples is a source of interest and active research.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An MRL of 5×10^{-6} mg chromium(VI)/m³ has been derived for intermediate- and chronic-duration inhalation exposure to chromium(VI) as chromium trioxide mist and other dissolved hexavalent chromium aerosols and mists. The MRL is based on a LOAEL of 0.002 mg chromium(VI)/m³ for upper respiratory effects in humans in the occupational exposure study by Lindberg and Hedenstierna (1983), which spanned both intermediate and chronic durations.

An MRL of 0.0003 mg chromium(VI)/m³ has been derived for intermediate-duration inhalation exposure to chromium(VI) as particulate hexavalent chromium compounds. The MRL is based on a benchmark concentration of 0.016 mg chromium(VI)/m³ for increases in lactate dehydrogenase activity in bronchoalveolar fluid from rats in the study by Glaser et al. (1990).

An MRL of 0.005 mg chromium(VI)/kg/day has been derived for intermediate-duration oral exposure to hexavalent chromium compounds for hematological effects (e.g., microcytic, hypochromic anemia) in rats using data from a study by NTP (2008a). Because several hematological parameters are used to define the clinical picture of anemia, the MRL is based on the average BMDL_{2sd} values for hemoglobin, MCV, and MCH of 0.52 mg chromium(VI)/kg/day.

An MRL of 0.0009 mg chromium(VI)/kg/day has been derived for chronic-duration oral exposure to hexavalent chromium compounds. The MRL is based on a benchmark dose of 0.09 mg chromium(VI)/kg/day for diffuse epithelial hyperplasia of the duodenum in mice in a study by NTP (2008a).

An MRL of 0.005 mg chromium(III)/m³ has been derived for intermediate-duration inhalation exposure to insoluble trivalent chromium particulate compounds. The MRL is based on a minimal LOAEL of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in rats in the study by Derelanko et al. (1999).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

An MRL of 0.0001 mg chromium(III)/m³ has been derived for intermediate-duration inhalation exposure to soluble trivalent chromium particulate compounds. The MRL is based on a LOAEL of 3 mg chromium(III)/m³ for nasal and larynx lesions in rats in the study by Derelanko et al. (1999).

A chronic oral reference dose (RfD) of 0.003 mg chromium(VI)/kg/day has been derived and verified by EPA for soluble salts of chromium(VI) (e.g., potassium chromate, sodium chromate, potassium dichromate, and sodium dichromate) (IRIS 2008). The RfD is based on a NOAEL for systemic effects in rats exposed to 2.5 mg chromium(VI)/kg/day as potassium chromate in the drinking water for 1 year in the study by MacKenzie et al. (1958).

A chronic inhalation RfC of 0.008 µg chromium(VI)/m³ has been derived and verified by EPA for chromic acid mists and dissolved chromium(VI) aerosols (IRIS 2008). The RfC is based on a LOAEL for nasal septum atrophy in workers exposed to 0.002 mg chromium(VI)/m³ (Lindberg and Hedenstierna 1983).

A chronic inhalation RfC of 0.0001 mg chromium(VI)/m³ has been derived and verified by EPA for chromium(VI) particulates (IRIS 2008). The RfC is based on a benchmark concentration of 0.016 mg chromium(VI)/m³ derived from data for lactate dehydrogenase activity in bronchoalveolar lavage fluid in rats exposed to sodium dichromate (Glaser et al. 1990).

A chronic oral RfD of 1.5 mg chromium(III)/kg/day has been derived and verified by EPA for insoluble salts of chromium(III) (e.g., chromium oxide and chromium sulfate) (IRIS 2008). The RfD is based on a NOAEL for systemic effects in rats fed 1,800 mg chromium(III)/kg/day for 5 days/week for 600 feedings (840 total days) in the study by Ivankovic and Preussmann (1975). EPA has determined that the data are inadequate for the development of an RfC for chromium(III) due to the lack of relevant toxicity study addressing the respiratory effects of chromium(III) (IRIS 2008).

The Institute of Medicine (IOM) of the National Academy of Sciences (NAS) determined an adequate intake (e.g., a level typically consumed by healthy individuals) of 20–45 µg chromium(III)/day for adolescents and adults (IOM 2001)

The international and national regulations, advisories, and guidelines regarding chromium in air, water, and other media are summarized in [Table 8-1](#).

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2008
	Chromium, metallic	Group 3 ^a	
	Chromium (III) compounds	Group 3 ^a	
	Chromium (VI)	Group 1 ^b	
WHO	Air quality guidelines		WHO 2000
	Chromium (VI)	1 µg/m ³ for a lifetime risk of 4x10 ⁻²	
	Drinking water quality guidelines		WHO 2004
	Chromium (for total chromium)	0.05 mg/L ^c	
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2007
	Calcium chromate (as Cr)	0.001 mg/m ³	
	Chromium and inorganic compounds (as Cr)		
	Metal and chromium (III) compounds	0.5 mg/m ³	
	Water-soluble chromium (VI) compounds	0.05 mg/m ³	
	Insoluble chromium (VI) compounds	0.01 mg/m ³	
	Lead chromate		
	As Pb	0.05 mg/m ³	
	As Cr	0.012 mg/m ³	
	Strontium chromate (as Cr)	0.0005 mg/m ³	
	Zinc chromates (as Cr)	0.01 mg/m ³	
	TLV basis (critical effects)		
	Calcium chromate (as Cr)	Lung cancer	
	Chromium		
	Metal and chromium (III) compounds	Upper respiratory tract and skin irritation	
	Water-soluble chromium (VI) compounds	Upper respiratory tract irritation and cancer	
	Insoluble chromium (VI) compounds	Lung cancer	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL (cont.)			
ACGIH	TLV basis (critical effects)		ACGIH 2007
	Lead chromate	Male reproductive damage, teratogenic effects, and vasoconstriction	
	As Pb		
	As Cr		
	Strontium chromate (as Cr)	Cancer	
EPA	Zinc chromates (as Cr)	Nasal cancer	
	AEGL-1, -2, and -3	No data	EPA 2007a
	Second list of AEGL priority chemicals for guideline development		EPA 2008a
	Chromium (III) chloride	Yes	
	Hazardous air pollutant		EPA 2007b
NIOSH	Chromium compounds	Yes	42 USC 7412
	REL (8-hour TWA)		NIOSH 2005
	Chromium, metal, chromium (II), and chromium (III) compounds	0.5 mg/m ³	
	REL (10-hour TWA)		
	Chromium (VI) trioxide (as Cr) ^{d,e}	0.001 mg/m ³	
	IDLH		
	Chromium, metal (as Cr)	250 mg/m ³	
	Chromium (VI) trioxide (as chromium [VI]) ^e	15 mg/m ³	
	Target organs		
	Chromium, metal	Eyes, skin, and respiratory system	
	Chromium (VI) trioxide	Blood, respiratory system, liver, kidneys, eyes, and skin	
	Category of pesticides		NIOSH 1992
	Potassium chromate	Group 1 pesticide	
	Potassium dichromate	Group 1 pesticide	
	Sodium chromate	Group 1 pesticide	
OSHA	PEL (8-hour TWA) for general industry (ceiling limit)		OSHA 2007a 29 CFR 1910.1000, Table Z-2
	Chromium (II) compounds (as Cr)	0.5 mg/m ³	
	Chromium (III) compounds (as Cr)	0.5 mg/m ³	
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m ³	,
	Chromium (VI) compounds	5 µg/m ³	OSHA 2007d 29 CFR 1910.1026

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference	
NATIONAL (cont.)				
OSHA	PEL (8-hour TWA) for shipyard industry (ceiling limit)		OSHA 2007c 29 CFR 1915.1000	
	Chromium (II) compounds (as Cr)	0.5 mg/m ³		
	Chromium (III) compounds (as Cr)	0.5 mg/m ³		
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m ³		
	Chromium (VI) compounds	0.5 µg/m ³	OSHA 2007e 29 CFR 1915.1026	
	PEL (8-hour TWA) for construction industry (ceiling limit)		OSHA 2007b 29 CFR 1926.55, Appendix A	
	Chromium (II) compounds (as Cr)	0.5 mg/m ³		
	Chromium (III) compounds (as Cr)	0.5 mg/m ³		
	Chromium metal and insoluble salt (as Cr)	1.0 mg/m ³		
	Chromium (VI) compounds	0.5 µg/m ³	OSHA 2007f 29 CFR 1926.1126	
	b. Water			
	EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
		Ammonium dichromate	Yes	
		Calcium chromate	Yes	
Chromium (III) sulfate		Yes		
Potassium chromate		Yes		
Strontium chromate		Yes		
Drinking water standards and health advisories			EPA 2006a	
Chromium (total)				
1-day health advisory for a 10-kg child		1 mg/L		
10-day health advisory for a 10-kg child		1 mg/L		
DWEL		0.1 mg/L		
Lifetime		No data		
National secondary drinking water standards			EPA 2003	
Chromium (total)				
MCL		0.1 mg/L		
Public health goal		0.1 mg/L		

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	National recommended water quality criteria ^g	No data	EPA 2006b
	Chromium (III)		
	Freshwater CMC	570 µg/L	
	Freshwater CCC	74 µg/L	
	Chromium (VI)		
	Freshwater CMC	16 µg/L	
	Freshwater CCC	11 µg/L	
	Saltwater CMC	1,100 µg/L	
	Saltwater CCC	50 µg/L	
	Toxic pollutants designated pursuant to Section 307(a)(1) of the Clean Water Act		EPA 2008i 40 CFR 401.15
	Chromium and compounds	Yes	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008c 40 CFR 117.3
	Chromium (III) sulfate	100 pounds	
c. Food	Potassium chromate	10 pounds	
	Strontium chromate	10 pounds	
EPA	Inert ingredients permitted for use in nonfood use pesticide products		EPA 2008e
	Chromium (III) oxide	Yes	
	Sodium chromate	Yes	
FDA	Bottled drinking water		FDA 2007a 21 CFR 165.110
	Chromium	0.1 mg/L	
	EAFUS ^h	No data	FDA 2008
	Indirect food additives: adhesives and components of coatings		FDA 2007b 21 CFR 175.105
	Sodium chromate	Yes	
	Recommended daily intake		FDA 2007c 21 CFR 101.9
	Chromium	120 µg	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Calcium chromate (as Cr)	A2 ⁱ	
	Chromium		
	Metal and chromium (III) compounds	A4 ^j	
	Water-soluble chromium (VI) compounds	A1 ^k	
	Insoluble chromium (VI) compounds	A1 ^k	
	Lead chromate		
	As Pb	A2 ⁱ	
	As Cr	A2 ⁱ	
	Strontium chromate (as Cr)	A2 ⁱ	
	Zinc chromates (as Cr)	A1 ^k	
	Biological exposure indices		
	Chromium		
	Water-soluble chromium (VI) fume		
	Total chromium in urine at end of shift at end of workweek	25 µg/L	
	Total chromium in urine increase during shift	10 µg/L	
EPA	Carcinogenicity classification		IRIS 2008
	Chromium(III), insoluble salts	Group D ^l	
	Chromium (VI)		
	Inhalation route of exposure	Group A ^m	
	Oral route of exposure	Group D ^l	
	RfC		
	Chromium(III), insoluble salts	Not available	
	Chromium (VI)		
	Chromic acid mists and dissolved Cr (VI) aerosols	8x10 ⁻⁶ mg/m ³	
	Cr(VI) particulates	1x10 ⁻⁴ mg/m ³	
	RfD		
	Chromium(III), insoluble salts	1.5 mg/kg/day	
	Chromium (VI)	3x10 ⁻³ mg/kg/day	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
EPA	Master Testing List	Yes ⁿ	EPA 2008f
	RCRA waste minimization PBT priority chemical list		EPA 1998c 63 FR 60332
	Chromium	Yes	
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list		EPA 2008d 40 CFR 264, Appendix IX
	Chromium (total)	Yes	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008j 40 CFR 302.4
	Ammonium dichromate	Yes ^o	
	Calcium chromate	Yes ^{o,p}	
	Chromium	Yes ^q	
	Chromium and compounds	Yes ^r	
	Chromium (III) sulfate	Yes ^o	
	Potassium chromate	Yes ^o	
	Strontium chromate	Yes ^o	
	Superfund, emergency planning, and community right-to-know		
	Reportable quantity		EPA 2008j 40 CFR 302.4
	Ammonium dichromate	10 pounds	
	Chromium	5,000 pounds	
	Calcium chromate	10 pounds	
	Chromium and compounds	None ^s	
	Chromium (III) sulfate	1,000 pounds	
	Potassium chromate	10 pounds	
	Strontium chromate	10 pounds	
	Effective date of toxic chemical release reporting		EPA 2008h 40 CFR 372.65
	Chromium	01/01/1987	
	Extremely Hazardous Substances		EPA 2008g 40 CFR 355, Appendix A
	Chromium (III) chloride		
	Reportable quantity	1 pound	
	Threshold planning quantity	1,000 pounds	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Chromium

Agency	Description	Information	Reference
NATIONAL (cont.)			
NTP	Carcinogenicity classification		NTP 2005
	Chromium (VI) compounds	Known to be human carcinogens	
	Calcium chromate		
	Chromium (VI) trioxide		
	Ferrochromite		
	Lead chromate		
	Strontium chromate		
	Zinc chromate		

^aGroup 3: The agent is not classifiable as to its carcinogenicity to humans.

^bGroup 1: The agent is carcinogenic to humans.

^cProvisional guideline value, as there is evidence of a hazard, but the available information on health effects is limited.

^dThe NIOSH REL (10-hour TWA) is 0.001 mg Cr(VI)/m³ for all hexavalent chromium (Cr(VI)) compounds. NIOSH considers all chromium (VI) compounds (including chromic acid, tert-butyl chromate, zinc chromate, and chromyl chloride) to be potential occupational carcinogens.

^eNIOSH potential occupational carcinogen.

^fGroup 1 pesticides: contains the pesticides that pose a significant risk of adverse acute health effects at low concentrations.

^gThe CMC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed briefly without resulting in an unacceptable effect. The CCC is an estimate of the highest concentration of a material in surface water to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect.

^hThe EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

ⁱA2: Suspected human carcinogen.

^jA4: Not classifiable as a human carcinogen.

^kA1: Confirmed human carcinogen.

^lGroup D: not classified as to its human carcinogenicity.

^mGroup A: known human carcinogen by the inhalation route of exposure.

ⁿChromium was recommended to the MTL by ATSDR in 1994 and the testing needs development is currently underway. The testing needs include acute toxicity, neurotoxicity, reproductive, and immunotoxicity health effects.

^oDesignated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.

^pDesignated CERCLA hazardous substance pursuant to Section 3001 of the Resource Conservation and Recovery Act.

^qDesignated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water.

^rDesignated CERCLA hazardous substance pursuant to Section 307(a) of the Clean Water Act and Section 112 of the Clean Air Act.

^sIndicates that no reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CCC = Criterion Continuous Concentration; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; CMC = Criteria Maximum Concentration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MTL = Master Testing List; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSD = transport, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1^* —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose₍₅₀₎ (TD₅₀)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

APPENDIX A

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences (proposed), Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(VI) aerosols and mists
CAS number: 18540-29-9
Date: June 2012
Profile status: Third Draft Post-Public Comment
Route: ☒ Inhalation ☐ Oral
Duration: ☐ Acute ☒ Intermediate ☒ Chronic
Key to figure: 11, 29
Species: Human

Minimal Risk Level: 5×10^{-6} mg chromium(VI)/m³ for dissolved hexavalent chromium aerosols and mists.

Reference: Lindberg E, Hedenstierna G. 1983. Chrome plating: Symptoms, findings in the upper airways, and effects on lung function. Arch Environ Health 38:367-374.

Experimental design: Eighty-five male and 19 female chrome-plating workers exposed to chromic acid were assessed for nose, throat, and chest symptoms, were inspected for effects in nasal passages, and were given pulmonary function tests. Study participants were compared to a reference group of 119 auto mechanics who were not exposed to chromium. The length of worker exposures to chromic acid ranged from 0.1 to 36 years, spanning intermediate- and chronic-exposure durations. Since the study population included workers exposed for both intermediate and chronic durations, data are considered appropriate for derivation of the intermediate- and chronic-duration inhalation MRLs. Chromium exposures were measured using personal air samplers and stationary equipment positioned close to the baths containing chromic acid. The exposure categories were defined as high average daily concentrations >0.002 mg chromium(VI)/m³, low (average daily concentrations <0.002 mg chromium(VI)/m³), and mixed category (chromium(VI) was <0.002 mg chromium(VI)/m³, with exposure to other acids and metallic salts). Correlations with nasal irritation and respiratory functions were also determined for peak exposures. Statistical analyses were performed using the chi-square test with Yate's correction when comparing nasal findings, and the Student's two tail t-test was used when comparing lung function findings.

Effects noted in study and corresponding doses: Nasal irritation ($p < 0.05$), mucosal atrophy ($p < 0.05$), and ulceration ($p < 0.01$), and decreases in spirometric parameters (forced vital capacity, forced expired volume in 1 second, and forced mid-expiratory flow) were observed in workers occupationally exposed to ≥ 0.002 mg chromium(VI)/m³ as chromic acid with a median exposure period of 2.5 years. About 60% of the exposed subjects were smokers, but no consistent association between exposure and cigarette smoking was observed. Short-term peak exposures to chromic acid correlated better with nasal septum damage than with 8-hour mean concentrations.

Dose end point used for MRL derivation: 0.002 mg chromium(VI)/m³ (nasal irritation, mucosal atrophy, decreased FVC, FEP₁, and FEV)

☐ NOAEL ☒ LOAEL ☐ benchmark concentration (BMC)

The LOAEL of 0.002 mg chromium(VI)/m³ for upper respiratory effects was selected as the point of departure for derivation of the intermediate- and chronic-duration inhalation MRLs for dissolved hexavalent chromium aerosols and mists. The LOAEL was duration-adjusted to a LOAEL_{ADJ} of 0.0005 mg chromium(VI)/m³ for continuous exposure. The intermediate- and chronic-duration inhalation MRLs of 0.000005 mg chromium(VI)/m³ for dissolved hexavalent chromium aerosols and mists were

derived by dividing the $LOAEL_{ADJ}$ of 0.0005 mg chromium(VI)/m³ by a composite uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Uncertainty factors used in MRL derivation:

[X] 10 for use of a LOAEL

[] 10 for extrapolation from animals to humans

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: No. Not applicable.

Was a conversion used from intermittent to continuous exposure? Yes, the LOAEL of 0.002 mg chromium(VI)/m³ was multiplied by 8 hour/24 hour and by 5 days/7 days to yield a duration-adjusted LOAEL ($LOAEL_{ADJ}$) of 0.0005 mg chromium(VI)/m³.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. In workers exposed to dissolved hexavalent chromium aerosols and mists (as chromium trioxide mist) for intermediate durations, nasal irritation, ulceration, and mucosal atrophy and rhinorrhea have been reported, with LOAEL values ranging from 0.09 to 0.1 mg chromium(VI)/m³ (Gibb et al. 2000a; Gomes 1972; Kleinfeld and Rosso 1965). Similarly, studies in rats and mice have shown that the upper respiratory tract is a primary target of exposure to inhaled chromium trioxide mist, with LOAEL values ranging from 0.49 to 3.63 mg chromium(VI)/m³ (Adachi 1987; Adachi et al. 1986; Kim et al. 2004). In addition, numerous intermediate- and chronic-duration exposure studies of workers to chromium(VI) compounds in general identify the respiratory tract as the primary target of exposure, with reports of epistaxis, chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, perforations and ulceration of the nasal septum, bronchitis, pneumoconiosis, decreased pulmonary function, and pneumonia (Bovet et al. 1977; Cohen et al. 1974; Davies et al. 1991; Gomes 1972; Greater Tokyo Bureau of Hygiene 1989; Hanslian et al. 1967; Keskinen et al. 1980; Kleinfeld and Rosso 1965; Lee and Goh 1988; Letterer 1939; Lieberman 1941; Lindberg and Hedenstierna 1983; Lucas and Kramkowski 1975; Mancuso 1951; Meyers 1950; Novey et al. 1983; Pastides et al. 1991; PHS 1953; Royle 1975b; Sassi 1956; Sluis-Cremer and du Toit 1968; Sorahan et al. 1987; Taylor 1966).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(VI) particulates
CAS number: 18540-29-9
Date: June 2012
Profile status: Third Draft Post-Public Comment
Route: ☒ Inhalation ☐ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Key to figure: 14
Species: Rat

Minimal Risk Level: 0.0003 mg chromium(VI)/m³ for hexavalent chromium particulate compounds

Reference: Glaser U, Hochrainer D, Steinholf D. 1990. Investigation of irritating properties of inhaled CrVI with possible influence on its carcinogenic action. Environ Hyg 2:235-245.

Experimental design: Eight-week-old male Wistar rats (30 animals in each group) were exposed 22 hours/day, 7 days/week to 0, 0.05, 0.1, 0.2, or 0.4 mg chromium(VI)/m³ as sodium dichromate aerosol particulates. Groups of 10 animals were sacrificed after 30 or 90 days of exposure or after 90 days of exposure and a 30-day recovery period. The respective mass median mean diameters (MMAD) and geometric standard deviation were 0.28 µm and 1.63 for the 0.5 and 0.1 mg chromium(VI)/m³ concentrations and 0.39 µm and 1.72 for the 0.2 and 0.4 mg chromium(VI)/m³ concentrations. Hematological, clinical chemistry, and urinalysis tests were performed. Gross and histological examinations were limited to the upper airway epithelia, left lung lobes, and the kidneys. In addition, lung lavage fluid was analyzed for total protein, albumin, lactate dehydrogenase, and β-glucuronidase activities.

Effects noted in study and corresponding doses: No deaths or abnormal clinical signs occurred at any of the exposures. Body weight was significantly (p<0.001) decreased at 0.2 and 0.4 mg chromium(VI)/m³ for 30 days, at 0.4 mg chromium(VI)/m³ for 90 days (p<0.05), and at 0.2 (p<0.01) and 0.4 mg chromium(VI)/m³ (p<0.05) in the recovery group. No differences in urinary protein and no exposure-related histopathological lesions were noted. No differences were seen in analysis of serum levels or activities of alanine aminotransferase, alkaline phosphatase, glucose, urea, total bilirubin, total cholesterol, or phospholipids. There were no hematological effects on red blood cells, but the white blood cell counts increased significantly in a dose-related manner at ≥0.1 mg chromium(VI)/m³ after 30 days and at ≥0.05 mg chromium(VI)/m³ after 90 days. White blood cells counts were not increased in 90 day exposure plus 30-day observation group.

Obstructive respiratory dyspnea occurred at ≥0.2 mg chromium(VI) chromium(VI)/m³ after 30 and 90 days. Mean lung weight was increased in all exposure groups and was statistically increased at ≥0.05 mg chromium(VI)/m³ for 30 days, and at ≥0.1 mg chromium(VI)/m³ for 90 days and in the 90-day plus recovery period group. Histological examination revealed slight hyperplasia in high incidence at ≥0.05 mg chromium(VI)/m³ at 30 days. With longer exposure, the incidence declined, indicating repair. Lung fibrosis occurred at ≥0.1 mg chromium(VI)/m³ for 30 days, but was not seen in rats exposed for 90 days. Accumulation of macrophages was observed in all exposed rats, regardless of exposure concentration or duration. This histiocytosis probably accounts for the increased lung weight. Histology of upper airways revealed focal inflammation. Results of bronchoalveolar lavage (BAL) analysis provided further information of the irritation effect. Total protein in BAL fluid was significantly increased in all exposed groups, but declined in the recovery period. Albumin in BAL fluid increased in a dose-related manner at all concentrations in the 30-day group, but recovery started during 90-day exposure and continued during the 30-day observation period. The activities of lactate dehydrogenase

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and β -glucuronidase, measures of cytotoxicity, were elevated at 0.2 and 0.4 mg chromium(VI)/m³ for 30 and 90 days, but returned to control values during the recovery period. The number of macrophages in the BAL fluid had significantly increased after 30 and 90 days, but normalized during the recovery period. The macrophages were undergoing cell division or were multinucleate and larger. This activation of macrophages was not observed in the recovered rats. The study authors concluded that inflammation is essential for the induction of most chromium inhalation effects and may influence the carcinogenicity of chromium(VI) compounds.

Dose end point used for MRL derivation: 0.016 mg/m³ (alterations in lactate dehydrogenase levels in bronchoalveolar lavage), converted to a BMCL_{HEC} of 0.010 mg chromium(VI)/m³

[] NOAEL [] LOAEL [X] benchmark concentration (BMC)

The Agency adopted the benchmark concentration (BMC) analysis of the Glaser et al. (1990) data conducted by Malsch et al. (1994) for deriving an intermediate-duration inhalation MRL for hexavalent chromium particulate compounds. Using the 90-day exposure data (as described above), Malsch et al. (1994) developed BMCLs for lung weight and BAL fluid levels of lactate dehydrogenase, protein, and albumin. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure. Duration-adjusted data were then fitted to a polynomial mean response regression model by the maximum likelihood method to derive BMCLs (defined as the 95% lower confidence limit on the concentration corresponding to a 10% relative change in the end point compared to the control). The BMCL values for lung weight, lactate dehydrogenase in the BAL fluid, protein in BAL fluid, and albumin in BAL fluid were 0.067, 0.016, 0.035, and 0.031 mg chromium(VI)/m³, respectively. The lowest BMCL, 0.016 mg chromium(VI)/m³ for alterations in lactate dehydrogenase levels in BAL fluid, was selected to derive the intermediate-duration inhalation MRL. The BMCL of 0.016 mg chromium(VI)/m³ was converted to a human equivalent concentration (BMCL_{HEC}) of 0.010 mg chromium(VI)/m³, as described below. The intermediate-duration inhalation MRL of 0.0003 mg chromium(VI)/m³ for hexavalent chromium particulate compounds was derived by dividing the BMCL_{HEC} of 0.010 mg chromium(VI)/m³ by a composite uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

Uncertainty factors used in MRL derivation:

[] 10 for use of a LOAEL

[X] 3 for extrapolation from animals to humans, with dosimetric adjustments

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The BMCL of 0.016 mg chromium(VI)/m³ was converted to a human equivalent concentration (BMCL_{HEC}) of 0.010 mg chromium(VI)/m³ using the RDDR (regional deposited dose ratio) program (EPA 1994c) as follows:

$$\text{BMCL}_{\text{HEC}} = \text{BMCL} \times \text{RDDR}$$

$$\text{BMCL}_{\text{HEC}} = 0.016 \text{ mg chromium(VI)/m}^3 \times 0.630 = 0.010 \text{ mg chromium(VI)/m}^3$$

where

RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR

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multiplier of 0.630 for the thoracic region tract was determined using the default subchronic body weight of 217 g for male Wistar rats (EPA 1988d) and a particle size MMAD \pm GSD of 0.5 \pm 1.63 μ m reported in the Glaser et al. (1984) study. Although the actual mean particle size reported in the critical study was 0.28 μ m, the RDDR program (EPA 1994c) can only run be run for particle sizes ranging from 0.5 to 30 μ m; therefore, 0.5 μ m was used as the default particle size to calculated the RDDR. Since the critical study did not report body weight, the default subchronic body weight of 217 g for male Wistar rats was used.

Was a conversion used from intermittent to continuous exposure? Yes. Animals were exposed for 22 hours/day, 7 days/week. Prior to conducting the benchmark analysis, Malsch et al. (1994) adjusted the dose-response data for intermittent exposure (22 hours/day) by multiplying data points for all outcome measures by 22 hours/24 hours.

Other additional studies or pertinent information that lend support to this MRL: The findings in this study are supported by another 90-day study conducted by the same group (Glaser et al. 1985). In this study, groups of 20 male Wistar rats were exposed to 0, 0.025, 0.05, 0.1, or 0.2 mg chromium(VI)/m³ as sodium dichromate for 22 hours/day, 7 days/week for 90 days. No deaths occurred at any of the exposures. All exposed animals showed normal histologic findings in lung, kidney, liver, stomach, and gonads. Lung and spleen weights were increased significantly at doses above 0.025 mg chromium(VI)/m³. Serum levels of triglycerides and phospholipid were increased in rats exposed to 0.2 mg chromium(VI)/m³. Serum contents of total immunoglobulins were significantly increased in the 0.05 and 0.1 mg chromium(VI)/m³ groups. At 0.025 and 0.2 mg chromium(VI)/m³, serum immunoglobulin contents were no different than controls. The SRBC antibody response was increased in all dosed groups over control values. Chromium treatment at 0.2 mg chromium(VI)/m³ also enhanced the mitogenic-stimulation of splenic Concanavalin T-lymphocytes. At 0.025 mg chromium(VI)/m³, there were significant increases in polynuclear macrophages and the number of macrophages in telophase, and increases in lymphocytes in bronchoalveolar lavage samples. At 0.05 and 0.2 mg chromium(VI)/m³, there were significant decreases in total numbers of macrophages. The percentages of polynuclear macrophages, lymphocytes, and granulocytes were increased at chromium exposures of 0.05 mg chromium(VI)/m³, but at 0.2 mg chromium(VI)/m³, the percentage of granulocytes cells was lower than control values. At 0.025 and 0.05 mg chromium(VI)/m³ exposures, phagocytosis of latex particles by alveolar macrophages was increased over controls. However, at 0.2 mg chromium(VI)/m³, the phagocytic activity was less than controls and there was a decrease in lung clearance of iron oxide particulates.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chromium(VI)
CAS Numbers: 18540-29-9
Date: June 2012
Profile status: Third Draft Post-Public Comment
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Graph Key: 48
Species: Rat

Minimal Risk Level: 0.005 ☒ mg chromium(VI)/kg/day ☐ ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546.
http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf. August 13, 2008.

Experimental design: Male F344/N rats (6–7 weeks old) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Male rats (50/group) were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. In a subgroup of 10 male rats, blood was collected from the retroorbital sinus after exposure durations of 4 days, 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids). Clinical signs of toxicity were assessed over the course of exposure. NTP calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Since observations were made at various time points during the chronic study (e.g., 22 days to 1 year), rather than using different dosage scales for each observation and outcome in the dose-response modeling, time-averaged dosages for the chronic duration (i.e., 101 weeks) were used to represent the dosage received during the intermediate- (i.e., >2–<52 weeks) and chronic- (>2–101 weeks) duration periods. This is an approximation of the actual dosages received, which varied as a function of body weight, and therefore, time of observation, with the differences most pronounced at the earliest periods of the intermediate-duration exposure (e.g., 3–12 weeks). The rationale for this simplification of the dose-response analysis is as follows: (1) outcomes observed at specific time points in the study (e.g., blood effects) after the acute period (>2 weeks) were considered to be relevant to the entire intermediate-duration period (>2–<52 weeks), if observed at multiple observation times during the intermediate-duration period; (2) chronic duration dosages were nearly identical to the time-averaged dosages for intermediate-duration exposure (e.g., <12% difference in the rat study); and (3) the possible bias introduced into estimates of BMDLs as a result of using chronic-duration dosages to represent intermediate-duration dosages is small (<12%) and conservative (i.e., BMDLs based on the chronic-duration dosages may be slightly lower than BMDLs based on actual intermediate-duration dosages).

Effect noted in study and corresponding doses: No treatment-related clinical signs of toxicity were observed in rats over the course of this study. Hematological effects consistent with microcytic, hypochromic anemia were observed at all intermediate-duration time points (22 days to 6 months) in male rats exposed to sodium dichromate dihydrate in drinking water; severity exhibited dose-dependence. At the 22-day assessment in rats, decreases were observed in Hct, Hgb, MCV, and MCH at ≥ 0.77 mg chromium(VI)/kg/day; effects at higher doses included decreased MCHC and platelet count at ≥ 2.1 mg chromium(VI)/kg/day, and decreased erythrocyte and reticulocyte counts, and increased nucleated

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erythrocytes at 5.9 mg chromium(VI)/kg/day). At the 3-month assessment in rats, decreases were observed for MCV and MCH at ≥ 0.77 mg chromium(VI)/kg/day; effects at higher doses included decreased Hgb at ≥ 2.1 mg chromium(VI)/kg/day and decreased Hct and increased erythrocyte, reticulocyte, platelet, leukocyte, and segmented neutrophil counts at ≥ 5.9 mg chromium(VI)/kg/day. Increases in cell counts indicate a compensatory hematopoietic response to anemia. At 6 months in rats, decreased MCV, MCH, and MCHC were observed at ≥ 0.77 mg chromium(VI)/kg/day; at 5.9 mg chromium(VI)/kg/day, decreased Hgb was observed. For all intermediate-duration exposures (22 days to 6 months), NOAEL and LOAEL values in male rats for hematological effects were 0.21 and 0.77 mg chromium(VI)/kg/day, respectively. Although effects in rats were similar at the 22-day and 3-month assessments, NTP (2008a) concluded that effects were more severe at 22 days than at 3 months based on the magnitude of changes and the number of parameters affected in rats exposed to 0.77 mg chromium(VI)/kg/day. Effects at 6 months were less severe than those observed at the 22-day and 3-month assessments. Although the magnitude of the decreases in hematological parameters was small at 0.77 mg chromium(VI)/kg/day compared to the control group (6.1–10.6%), there is clear indication of damage to the hematological system and this dose level was considered a minimal LOAEL. At the next highest dose (2.1 mg chromium(VI)/kg/day), these parameters were 16–25% lower than controls. As defined by ATSDR, an effect that enhances the susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences should be considered adverse. Thus, the slight, but statistically significant, decrease in hematological parameters at 0.77 mg chromium(VI)/kg/day was considered minimally adverse.

Evaluation of clinical chemistry parameters in male rats showed significant alterations in serum liver enzyme activities, although changes were not consistent over all intermediate-duration exposures. At the 22-day assessment, increases were observed for ALT (≥ 0.77 mg chromium(VI)/kg/day) and AP (5.9 mg chromium(VI)/kg/day), but no change was observed for SDH. At 3 months, ALT was increased (≥ 0.77 mg chromium(VI)/kg/day), but AP was decreased (≥ 0.21 mg chromium(VI)/kg/day) and no change was observed for SDH. At 6 months, increases were observed for ALT and SDH (≥ 2.1 mg chromium(VI)/kg/day), but AP was decreased (0.77 mg chromium(VI)/kg/day). Due to the inconsistent changes in serum liver enzyme activities, NTP (2008a) concluded that alterations in liver enzymes (specifically ALT) were suggestive of enzyme induction, rather than hepatocellular damage. Thus, altered serum liver enzyme activities were not considered indicative of an adverse effect on the liver.

Dose and end point used for MRL derivation: 0.52 mg chromium(VI)/kg/day (microcytic, hypochromic anemia)

[] NOAEL [] LOAEL [X] benchmark dose (BMD)

Exposure to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia in male rats at all intermediate-duration exposures (22 days to 6 months). The severity was greatest at the 22-day assessment compared to the 3- and 6-month assessments; therefore, microcytic, hypochromic anemia observed at the 22-day assessment was identified as the critical effect for derivation of the intermediate-duration oral MRL. In male rats, decreases in Hct, Hgb, MCV, and MCH were the most sensitive measures of hematological effects, with NOAEL and LOAEL values of 0.21 and 0.77 mg chromium(VI)/kg/day, respectively; data sets for these end points are summarized in Table A-1.

Table A-1. Hematological Effects in Male F/344 Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

	Dose (mg chromium(VI)/kg/day)				
	0	0.21	0.77	2.1	5.9
Male rats					
Hematocrit (percent)	46.0±1.1 ^a	44.4±0.4	43.2±0.6 ^b	38.7±0.6 ^c	33.5±0.8 ^c
Hemoglobin (g/dL)	15.5±0.3	15.1±0.2	14.2±0.2 ^c	12.0±0.3 ^c	10.1±0.2 ^c
MCV (fL)	59.5±0.4	58.6±0.5	54.9±0.5 ^c	47.4±0.4 ^c	45.0±0.7 ^c
MCH (pg)	19.8±0.1	19.5±0.2	17.7±0.2 ^c	14.8±0.2 ^c	16.3±0.5 ^c

^aMean±standard error: number of rats/group=10; number of mice/group=10

^bSignificantly different ($p \leq 0.05$) from the control group by Dunn's or Shirley's test

^cSignificantly different ($p \leq 0.01$) from the control group by Dunn's or Shirley's test

MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume

Source: NTP 2008a

To determine the point of departure for derivation of the intermediate-duration oral MRL, available continuous-variable models in the EPA BMDs (version 1.4.1) were fit to the data for Hct, Hgb, MCV, and MCH in male rats (NTP 2008a; Table A-1). The BMD and the 95% lower confidence limit (BMDL) calculated is an estimate of the doses associated with a change of 2 standard deviations from the control (BMDL_{2sd}); the use of 2 standard deviations takes into consideration of the normal variability in the population and decreases the possibility of misclassifying a small change as anemia. The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDs to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMD derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMD modeling.

A summary of the BMDs and BMDLs for the best fitting models for each hematological end point are shown in Table A-2. For male rats, BMDL_{2sd} values ranged from 0.37 mg chromium(VI)/kg/day for MCH to 0.71 mg chromium(VI)/kg/day for hemoglobin. None of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis, for Hct. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Because several hematological parameters are used to define the clinical picture of anemia, the BMDL_{2sd} values for hemoglobin, MCV, and MCH were averaged resulting in a BMDL_{2sd} of 0.52 mg chromium(VI)/kg/day. The intermediate-duration MRL of 0.005 mg chromium(VI)/kg/day was derived by dividing the average BMDL_{2sd} by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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Table A-2. Summary of BMDs and BMDLs From the Best Fitting Models for Hematological End Points in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

End point	Model	Number of doses	BMD _{2sd} (mg/kg/day) ^b	BMDL _{2sd} (mg/kg/day) ^b
Hematocrit (percent) ^a	—	—	—	—
Hemoglobin (g/dL)	Polynomial (2-degree)	5	0.88	0.71
MCV (fL)	Hill	4	0.63	0.49
MCH (pg)	Linear	4	0.44	0.37

^aNone of the models provided an adequate fit to the data.

^bUnits of BMD_{1sd} and BMDL_{1sd} are mg chromium(VI)/kg/day.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; 2sd = a 2 standard deviation change from the control

Uncertainty Factors used in MRL derivation:

- [] 10 for use of a LOAEL
- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each exposure group based on measured body weight and drinking water intake were reported by study authors (NTP 2008a). Additional information on daily doses used for intermediate-duration exposure is discussed in the experimental design section above.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Identification of anemia, as defined by significant alterations in hematocrit, hemoglobin, MCH, and MCV, as the critical end point for deriving an intermediate-duration oral MRL is supported by results of a 22-day study in female mice (NTP 2008a), 3-month drinking water study on sodium dichromate dihydrate in rats and mice (NTP 2007), and dietary studies on potassium dichromate in rats and mice (NTP 1996a, 1996b, 1997). In the 3-month sodium dichromate dihydrate drinking water study in male and female F344/N rats (NTP 2007), blood was collected for hematology assessments after 23 days and after 3 months of exposure; for B6C3F1 mice, hematological assessments were conducted only after 3 months. Dose-dependent hematological effects consistent with microcytic, hypochromic anemia, including decreased Hct, Hgb, MCV, and MCH, were observed in rats at the 23-day and 14-week hematological assessments; the LOAEL value at both time points in males and females was 1.7 mg chromium(VI)/kg/day (a NOAEL was not established). Hematological effects were more severe at the 23-day assessment compared to the 14 week assessment. Similar hematological effects were observed in male and female B6C3F1 mice and male BALB/c and C57BL/6 mice exposed to sodium dichromate dihydrate in drinking water for 14 weeks, with a LOAEL value of 3.1 mg chromium(VI)/kg/day (a NOAEL was not established). Results of the 3-month study in rats and mice (NTP 2007) were not selected as the basis for the

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intermediate-duration MRL because a lower LOAEL value (0.77 mg chromium(VI)/kg/day) was observed for intermediate-duration exposures in the 2-year study (NTP 2008a). In a dietary studies on potassium dichromate, microcytic, hypochromic anemia was observed in male and female Sprague-Dawley rats exposed for 9 weeks, with NOAEL and LOAEL values in males of 2.1 and 8.4 mg chromium(VI)/kg/day, respectively, and of 2.5 and 9.8 mg chromium(VI)/kg/day, respectively, in females (NTP 1996b). Similar hematological effects were observed in male and female BALB/c mice exposed to potassium dichromate in the diet for 9 weeks with NOAEL and LOAEL values in males of 7.3 and 32.2 mg chromium(VI)/kg/day, respectively, and in females of 12 and 48 mg chromium(VI)/kg/day, respectively (NTP 1996a). In a multigeneration study on dietary potassium dichromate in BALB/c mice, a LOAEL value of 7.8 for hematological effects was reported (a NOAEL was not established) (NTP 1997). Compared to the LOAEL values for hematological effects at 22 days and 3 months in male rats (0.77 mg chromium(VI)/kg/day) and female mice (0.38 mg chromium(VI)/kg/day) observed in the critical study on sodium dichromate dihydrate in drinking water, higher LOAEL values were reported in the 9-week dietary study on potassium dichromate in rats (8.4 and 9.8 mg chromium(VI)/kg/day in males and females, respectively) (EPA 1996b) and mice (32.2 and 48 mg chromium(VI)/kg/day in males and females, respectively) (NTP 1996a). The reason for the differences in LOAEL values has not been established, but could be due to different exposure media (drinking water versus feed) or differences in strain sensitivity (rats).

The erythrocyte has a high capacity for chromium(VI) uptake and binding. Chromium(VI) enters the erythrocyte through a sulfate ion channel; once inside the cell, it is rapidly reduced to reactive intermediates (chromium(V) and chromium(IV)) and binds to hemoglobin and other ligands. The chromium-hemoglobin complex is stable and remains sequestered within the cell over the life-span of the erythrocyte (Paustenbach et al. 2003). Thus, chromium(VI) uptake and subsequent sequestration as a chromium-Hgb complex by erythrocytes provides supporting information regarding the plausibility of adverse hematological effects following intermediate-duration oral exposure to chromium(VI).

Details of Benchmark Dose Analysis for the Intermediate-duration Oral MRL

Hematocrit in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data (Table A-3). The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest doses were dropped from the data set. As with the full data set, statistical tests indicated that the variances were not constant across exposure groups without the highest doses. Similar to the full data set, applying the nonhomogenous variance model also did not provide an adequate fit (as assessed by the p-value for variance); therefore, the data set is considered not suitable for benchmark dose modeling.

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Table A-3. Model Predictions for Changes in Hematocrit (Percent) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

Model	Variance p-value ^a	p-Value for the means ^a	AIC	BMD _{2sd} (mg/kg/day)	BMDL _{2sd} (mg/kg/day)
All doses					
Linear ^{b,c}	0.03	0.02	145.49	—	—
Linear ^{c,d}	0.01	0.02	147.49	—	—
Polynomial (1-degree) ^{c,d}	0.01	0.02	147.49	—	—
Polynomial (2-degree) ^{c,d}	0.01	0.02	147.49	—	—
Polynomial (3-degree) ^{c,d}	0.01	0.02	147.49	—	—
Polynomial (4-degree) ^{c,d}	0.01	0.02	147.49	—	—
Power ^d	0.01	0.02	147.49	—	—
Hill ^d	0.01	0.28	142.76	—	—
Highest dose dropped					
Linear ^{b,c}	0.01	0.64	109.33	—	—
Linear ^{c,d}	0.02	0.43	109.21	—	—
Polynomial (1-degree) ^{c,d}	0.02	0.43	109.21	—	—
Polynomial (2-degree) ^{c,d}	0.02	0.43	109.21	—	—
Polynomial (3-degree) ^{c,d}	0.02	0.43	109.21	—	—
Power ^d	0.02	0.43	109.21	—	—
Hill ^d	0.02	0.21	111.09	—	F ^e
Two highest doses dropped					
Linear ^{b,c}	0.01	0.37	86.65	—	—
Linear ^{c,d}	0.02	0.15	85.61	—	—
Polynomial (1-degree) ^{c,d}	0.02	0.15	85.61	—	—
Polynomial (2-degree) ^{c,d}	0.02	0.15	85.61	—	—
Power ^d	0.02	0.15	85.61	—	—
Hill ^d	NA ^f				

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.^bConstant variance^cRestriction = non-positive^dNonconstant variance^eF = BMDL computation failed^fNA = model failed to generate output

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

Hemoglobin in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. Only the Hill model provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-4); however, the model failed to generate a figure. Without a visual representation of the model, an assessment of model fit is not complete. In order to obtain an appropriate

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assessment for model fit adequacy, the highest dose was dropped from the dataset. After dropping the highest dose from the dataset, all models provided an adequate fit to the constant variance model and to the means (as assessed by the p-values for variance and means). Most models, with the exception of the Hill model, took the form of a linear model. Comparing across models, the best fitting model is generally determined by the lowest AIC. As assessed by the AIC, the linear model provides the best fit to the data. The predicted BMD_{2sd} and BMDL_{2sd} for the data are 0.88 and 0.71 mg chromium(VI)/kg/day (Figure A-1).

Table A-4. Model Predictions for Changes in Hemoglobin (g/dL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

Model ^a	Variance p-value ^b	p-Value for the means ^b	AIC	BMD _{2sd} (mg/kg/day)	BMDL _{2sd} (mg/kg/day)
Linear ^c	0.40	<0.0001	46.98	—	—
Polynomial (1-degree) ^c	0.40	<0.0001	46.98	—	—
Polynomial (2-degree) ^c	0.40	<0.0001	46.98	—	—
Polynomial (3-degree) ^c	0.40	<0.0001	46.98	—	—
Polynomial (4-degree) ^c	0.40	<0.0001	46.98	—	—
Power	0.40	<0.0001	46.98	—	—
Hill	0.40	0.51	24.37	0.83	0.55
Highest dose dropped					
Linear	0.36	0.99	20.37	0.88	0.71
Polynomial (1-degree) ^c	0.36	0.99	20.37	0.88	0.71
Polynomial (2-degree) ^c	0.36	0.99	20.37	0.88	0.71
Polynomial (3-degree) ^c	0.36	0.99	20.37	0.88	0.71
Power	0.36	0.99	20.37	0.88	0.71
Hill	0.36	0.99	22.36	0.87	0.57

^aConstant variance assumed for all models

^bValues <0.1 fail to meet conventional goodness-of-fit criteria.

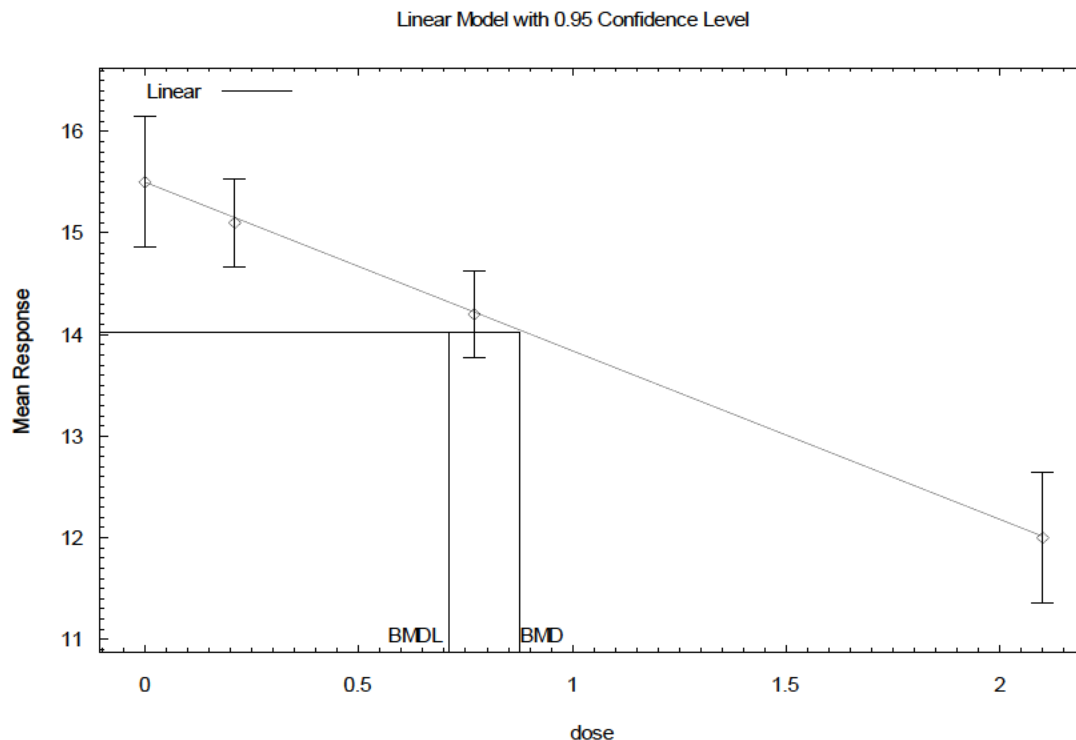
^cRestriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

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Figure A-1. Predicted and Observed Changes in Hemoglobin in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Mean Cell Volume in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did provide an adequate fit (as assessed by the p-value for variance) to the data. The polynomial, power, and Hill models were then fit to the data with constant variance assumed. The Hill model was the only model which provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-5). Using the constant-variance Hill model, the BMD_{2sd} and $BMDL_{2sd}$ are 0.63 mg chromium(VI)/kg and 0.49 mg chromium(VI)/kg, respectively (Figure A-2).

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Table A-5. Model Predictions for Changes in MCV (fL) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

Model ^a	Variance p-value ^b	p-Value for the means ^b	AIC	BMD _{2sd} (mg/kg/day)	BMDL _{2sd} (mg/kg/day)
Linear ^c	0.41	<0.0001	168.50	—	—
Polynomial (1-degree) ^c	0.41	<0.0001	168.50	—	—
Polynomial (2-degree) ^c	0.41	<0.0001	168.50	—	—
Polynomial (3-degree) ^c	0.41	<0.0001	168.50	—	—
Polynomial (4-degree) ^c	0.41	<0.0001	168.50	—	—
Power	0.41	<0.0001	168.50	—	—
Hill	0.41	0.41	104.52	0.63	0.49

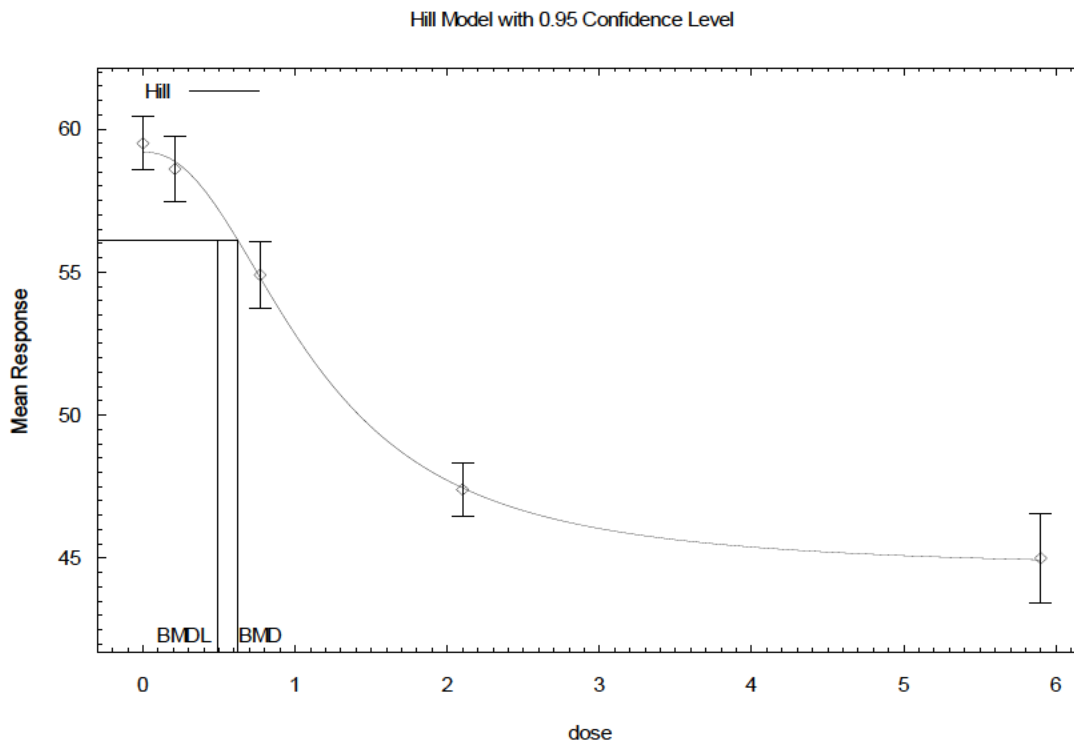
^aConstant variance assumed for all models^bValues <0.1 fail to meet conventional goodness-of-fit criteria.^cRestriction = non-positive

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

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Figure A-2. Predicted and Observed Changes in MCV in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



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*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day

Source: NTP 2008a

Mean Cell Hemoglobin in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model also did not provide an adequate fit (as assessed by the p-value for variance). In an attempt to achieve an adequate fitting model, the highest dose was dropped from the data-set. Unlike the full data-set, statistical tests indicated that the variances were constant across exposure groups without the highest dose. All of the models reverted to the linear model and provided an adequate fit to the means (Table A-6). Using the constant-variance Linear model (without the highest dose), the BMD_{2sd} and BMDL_{2sd} are 0.44 and 0.37 mg chromium(VI)/kg, respectively (Figure A-3).

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Table A-6. Model Predictions for Changes in MCH (pg) in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days

Model	Variance p-value ^b	p-Value for the means ^b	AIC	BMD _{2sd} (mg/kg/day)	BMDL _{2sd} (mg/kg/day)
All doses					
Linear ^{b,c}	<0.0001	<0.0001	107.27	—	—
Linear ^{c,d}	0.00	<0.0001	57.60	—	—
Polynomial (1-degree) ^{c,d}	0.00	<0.0001	57.60	—	—
Polynomial (2-degree) ^{c,d}	0.00	<0.0001	57.60	—	—
Polynomial (3-degree) ^{c,d}	0.00	<0.0001	57.60	—	—
Polynomial (4-degree) ^{c,d}	0.00	<0.0001	57.60	—	—
Power ^d	0.00	<0.0001	57.60	—	—
Hill ^d	0.00	0.02	34.64	—	—
Highest dose dropped (four doses)					
Linear^{b,c}	0.14	0.15	-3.57	0.44	0.37
Polynomial (1-degree) ^{b,c}	0.14	0.15	-3.57	0.44	0.37
Polynomial (2-degree) ^{b,c}	0.14	0.15	-3.57	0.44	0.37
Polynomial (3-degree) ^{b,c}	0.14	0.15	-3.57	0.44	0.37
Power ^b	0.14	0.15	-3.57	0.44	0.37
Hill ^b	0.14	NA ^e	-3.39	0.46	0.32

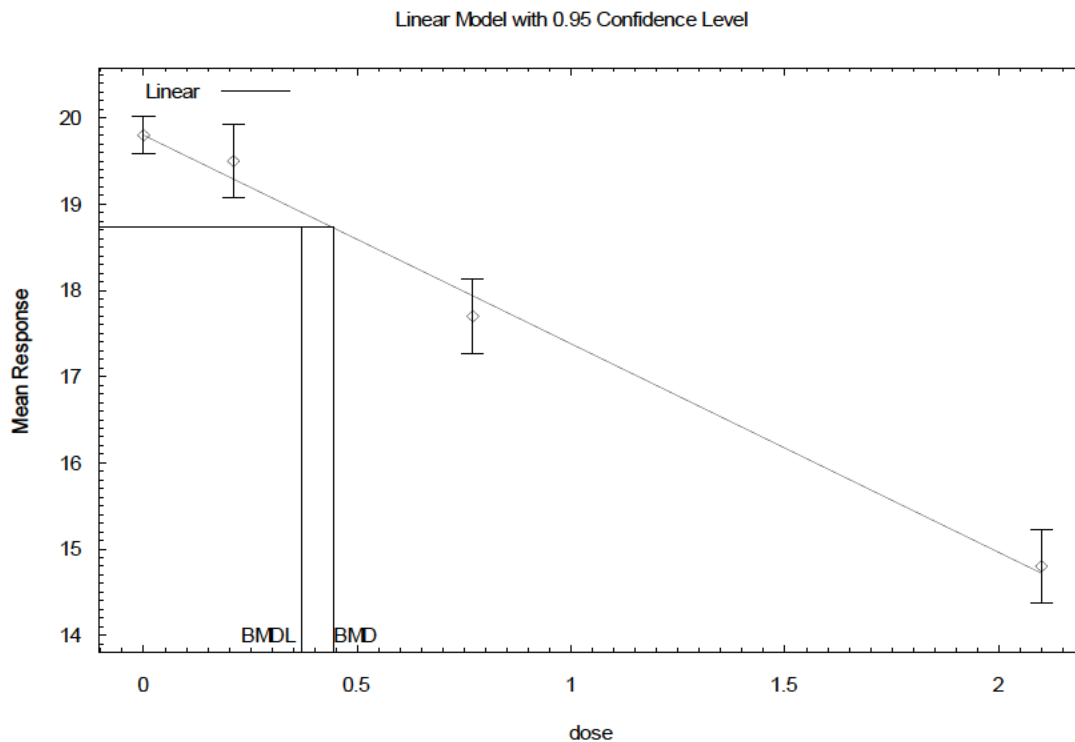
^aValues <0.1 fail to meet conventional goodness-of-fit criteria.^bConstant variance^cRestriction = non-positive^dNonconstant variance^eNA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; 2sd = a 2 standard deviation change from the control

Source: NTP 2008a

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Figure A-3. Predicted and Observed Changes in MCH in Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 22 Days*



*BMDs and BMDLs indicated are associated with a 2 standard deviation change from the control, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chromium(VI)
CAS Numbers: 18540-29-9
Date: June 2012
Profile status: Third Draft Post-Public Comment
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Graph Key: 109
Species: Mouse

Minimal Risk Level: 0.0009 ☒ mg chromium(VI)/kg/day ☐ ppm

Reference: NTP. 2008a. NTP technical report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate (CAS No. 7789-12-0) in F344/N rats and B6C3F1 mice (drinking water studies). Washington, DC: National Toxicology Program. NTP TR 546.
http://ntp.niehs.nih.gov/files/546_web_FINAL.pdf. August 13, 2008.

Experimental design: Groups of F344/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) were exposed to sodium dichromate dihydrate in drinking water in a 2-year toxicology and carcinogenicity study. Rats and female mice were exposed to drinking water concentrations of 0, 14.3, 57.3, 172, or 516 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male rats of 0, 0.6, 2.2, 6, or 17 mg/kg (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg chromium(VI)/kg/day, respectively), in female rats of 0, 0.7, 2.7, 7, or 20 mg/kg (equivalent to 0, 0.24, 0.94, 2.4, and 7.0 mg chromium(VI)/kg/day, respectively), and in female mice of 0, 1.1, 3.9, 9, or 25 mg/kg (equivalent to 0, 0.38, 1.4, 3.1, or 8.7 mg chromium(VI)/kg/day, respectively) over the course of the 2-year study. Male mice were exposed to 0, 14.3, 28.6, 85.7, or 257.4 mg sodium dichromate dihydrate/L. NTP (2008a) calculated mean daily doses of sodium dichromate dihydrate in male mice of 1.1, 2.6, 7, or 17 mg/kg (equivalent to 0, 0.38, 0.91, 2.4, and 5.9 mg chromium(VI)/kg/day, respectively). Mortality, clinical signs of toxicity, body weight, and water intake were assessed over the course of exposure. In a subgroup of 10 male rats and 10 female mice, blood was collected from the retroorbital sinus after exposure durations of 4 days (rats only), 22 days, 3 months, 6 months, and 1 year and evaluated for hematology (Hct; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; MCV; MCH; MCHC; and leukocyte count and differentials) in rats and mice and clinical chemistry (urea nitrogen, creatinine, total protein, albumin, ALT, AP, creatine kinase, SDH, and bile acids) in rats only. Blood for hematology and clinical chemistry was not obtained at the end of the 2-year treatment period. At the end of the 2-year treatment period, necropsies and histopathological assessment of comprehensive tissues, gross lesions and tissue masses were performed on all animals. No data on organ weights were presented in the study report (NTP 2008a).

Effect noted in study and corresponding doses: Study results presented in the following discussion are noncancer findings associated with chronic-duration exposures only; results of hematological and clinical chemistry assessments conducted at 4 days and from 22 days to 6 months are described in the acute- and intermediate-duration MRL worksheets, respectively; carcinogenic effects are reviewed in Section 3.2.2.7 (Oral Exposure, Cancer). In rats, no treatment-related effects were observed on survival and no clinical signs of toxicity were observed. Final body weight was significantly decreased by 12% in male and 11% in females exposed to the highest drinking water concentration. Study authors attributed alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in male rats at 1-year showed dose-dependent effects indicative of microcytic, hypochromic anemia: decreased MCH (≥ 0.77 mg chromium(VI)/kg/day), decreased MCV and MCHC (≥ 2.1 mg chromium(VI)/kg/day), and decreased Hgb (5.9 mg chromium(VI)/kg/day). No

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hematological effects were observed at 2.1 mg chromium(VI)/kg/day. Other hematological effects observed were decreased leukocyte (5.9 mg chromium(VI)/kg/day) and segmented neutrophil counts (≥ 0.77 mg chromium(VI)/kg/day). Alterations in clinical chemistry parameters observed after 1 year of exposure were increased ALT and decreased AP (≥ 0.77 mg chromium(VI)/kg/day), increased BUN and creatine kinase (≥ 2.1 mg chromium(VI)/kg/day), and decreased total protein (5.9 mg chromium(VI)/kg/day). Regarding the toxicological significance of elevated ALT, as discussed below, histopathological assessment of the liver showed minimal-to-mild chronic inflammation in males (≥ 2.1 mg chromium(VI)/kg/day) and females (≥ 0.24 mg chromium(VI)/kg/day). However, since serum activities of AP, SDH, or bile acids were not increased, elevated serum ALT activity may have resulted from enzyme induction rather than hepatocellular injury. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (males and females), small intestine (males and females), mesenteric lymph nodes (males and females), pancreatic lymph nodes (females only) and salivary gland (females only). Hepatic lesions observed in male rats included minimal-to-mild chronic inflammation (≥ 0.77 mg chromium(VI)/kg/day) and histiocytic cellular infiltration (5.9 mg chromium(VI)/kg/day); hepatic lesions in females included chronic inflammation (≥ 0.24 mg chromium(VI)/kg/day), histiocytic cellular infiltration (≥ 0.94 mg chromium(VI)/kg/day) and fatty change (≥ 0.94 mg chromium(VI)/kg/day). Although chronic hepatic inflammation is commonly observed in aging rats, the incidence was significantly enhanced by exposure. Histiocytic cellular infiltration (minimal-to-mild) of the duodenum, was observed in males (≥ 0.77 mg chromium(VI)/kg/day) and females (≥ 2.4 mg chromium(VI)/kg/day). Nonneoplastic lesions of lymph nodes included the following: histiocytic cellular infiltration of mesenteric lymph nodes in males and females at ≥ 0.77 and ≥ 2.4 mg chromium(VI)/kg/day, respectively; hemorrhage of mesenteric lymph nodes in males and females at ≥ 0.77 and ≥ 7.0 mg chromium(VI)/kg/day, respectively; and histiocytic cellular infiltration of pancreatic lymph nodes in females at ≥ 2.4 mg chromium(VI)/kg/day only. The incidence of salivary gland atrophy was significantly in female rats at 2.4 mg chromium(VI)/kg/day; although the incidence was also increased at 7.0 mg chromium(VI)/kg/day, the change was not significantly different from control. Salivary atrophy was not observed in male rats. No data on organ weights were presented in the study report (NTP 2008a).

In mice, no treatment-related effects on survival or signs of toxicity were observed. Final body weight was significantly decreased by 15% in male and 8% in females exposed to the highest drinking water concentration. The study authors attributed the alterations in body weight to decreased water intake (due to decreased palatability) rather than to a toxicological effect. Hematological assessments conducted in female mice at 1 year showed dose-dependent effects indicative of microcytic, hypochromic anemia and compensatory erythropoiesis: decreased MCV and MCH (≥ 3.1 mg chromium(VI)/kg/day) and increased erythrocyte count at ≥ 3.1 mg chromium(VI)/kg/day. Platelet count and segmented neutrophil count were decreased at 8.7 mg chromium(VI)/kg/day. Severity of hematological effects on mice was less than in rats. Clinical chemistry was not evaluated in male or female mice. Histopathological evaluations revealed an increased incidence of nonneoplastic lesions in the liver (females), small intestine (male and females), and mesenteric and pancreatic lymph nodes (males and females). Histiocytic cellular infiltration of the liver was observed in all treatment groups, with incidence and severity exhibiting dose-dependence. Chronic inflammation of the liver was also observed in females at ≥ 3.1 mg chromium(VI)/kg/day. In males, only pre-neoplastic (clear cell and eosinophilic foci) lesions were observed at the highest dose tested. Diffuse epithelial hyperplasia of the duodenum was observed in all treatment groups in males and females (≥ 0.38 mg chromium(VI)/kg/day), with histiocytic cellular infiltration of the duodenum in males and females at ≥ 2.4 and 3.1 mg chromium(VI)/kg/day, respectively. Histiocytic cellular infiltration was observed in mesenteric lymph nodes in all treatment groups in males and females (≥ 0.38 mg chromium(VI)/kg/day) and in pancreatic lymph nodes at ≥ 2.4 and ≥ 3.1 mg chromium(VI)/kg/day in males and females, respectively. Increased incidence of cytoplasm alteration of the pancreas (depletion of zymogen granules from acinar epithelial cells) was observed in males at ≥ 2.4 mg

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chromium(VI)/kg/day and in females in all treatment groups (≥ 0.38 mg chromium(VI)/kg/day); the toxicological significance of this finding is not clear.

Dose and end point used for MRL derivation: 0.09 mg chromium(VI)/kg/day (diffuse epithelial hyperplasia of the duodenum)

[] NOAEL [] LOAEL [X] benchmark dose (BMD)

Chronic-duration exposure of rats and mice to sodium dichromate dihydrate in drinking water resulted in microcytic, hypochromic anemia and nonneoplastic lesions of the liver, duodenum, mesenteric and pancreatic lymph nodes, pancreas and salivary gland. Based on comparison of LOAEL values (Table A-7), the lowest LOAELs were observed for histopathological changes of the liver (chronic inflammation in female rats and histiocytic cellular infiltration in female mice), duodenum (diffuse epithelial hyperplasia in male and female mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice) and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice), with effects occurring in all treatment groups. Therefore, all effects with LOAEL values of the lowest dose tested were considered as the possible the critical effect for derivation of the chronic-duration oral MRL. Incidence data for these lesions are summarized in Table A-8.

Table A-7. NOAEL and LOAEL Values for Effects in Rats and Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 1–2 Years

Effect or tissue with lesion	NOAEL/LOAEL value (mg chromium(VI)/kg/day)			
	Male rats	Female rats	Male mice	Female mice
Hematological effects	0.21/0.77	N/A	N/A	1.4/3.1
Liver	0.21/0.77	0.24 ^a	2.4/5.9 ^c	0.38 ^a
Duodenum	0.21/0.77	0.94/2.4	0.38 ^a	0.38 ^a
Mesenteric lymph node	0.21/0.77	0.94/2.4	0.38 ^a	0.38 ^a
Pancreatic lymph node	N/O	0.94/2.4	0.91/2.4	1.4/3.1
Pancreas	N/O	N/O	0.91/2.4	0.38 ^a
Salivary gland	N/O	2.4 ^b	N/O	N/O

^aNo NOAEL value was identified; effects occurred in all treatment groups

^bNot observed at other doses

^cPre-neoplastic lesions

LOAEL = lowest-observed-adverse-effect level; N/A = not assessed; N/O = effect not observed; NOAEL = no-observed-adverse-effect level

Source: NTP 2008a

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Table A-8. Incidence Data for Nonneoplastic Lesions^a Occurring in All Treatment Groups of Female F/344 Rats and Male and Female B6C3F1 Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

	Dose (mg chromium(VI)/kg/day)				
	0	0.24	0.94	2.4	7.0
Female rats					
Liver, chronic inflammation	12/50 ^b (1.3)	21/50 ^c (1.2)	28/50 ^d (1.3)	35/50 ^d (1.6)	39/50 ^d (2.1)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	0.91	2.4	5.9
Male mice					
Duodenum: diffuse epithelial hyperplasia	0/50	11/50 ^d (2.0)	18/50 ^d (1.6)	42/50 ^d (2.1)	32/50 ^c (2.1)
Mesenteric lymph node: histiocytic cellular infiltration	14/47 (1.2)	38/47 ^d (1.1)	31/49 ^d (1.2)	32/49 ^d (1.5)	42/46 ^c (2.5)
	Dose (mg chromium(VI)/kg/day)				
	0	0.38	1.4	3.1	8.7
Female mice					
Duodenum: diffuse epithelial hyperplasia	0/50	16/50 ^d (1.6)	35/50 ^d (1.7)	31/50 ^d (1.6)	42/50 ^d (2.2)
Mesenteric lymph node: histiocytic cellular infiltration	3/46 (1.0)	29/48 ^d (1.3)	26/46 ^d (1.1)	40/50 ^d (1.9)	42/50 ^d (2.7)
Liver: histiocytic cellular infiltration	2/49 (1.0)	15/50 ^d (1.1)	23/50 ^d (1.0)	32/50 ^d (1.0)	45/50 ^d (1.9)
Pancreas: acinus, cytoplasmic alteration	0/48	6/50 ^c (2.5)	6/49 ^c (2.0)	14/50 ^d (2.4)	32/50 ^d (2.6)

^aLesion severity (1=minimal, 2=mild, 3=moderate, 4=marked)

^bNumber of animals with lesions/number of animals examined

^cSignificantly different ($p \leq 0.05$) from the control group by Dunn's or Shirley's test

^dSignificantly different ($p \leq 0.01$) from the control group by Dunn's or Shirley's test

Source: NTP 2008a

To determine the specific end point for derivation of the chronic-duration oral MRL, all available dichotomous models in the EPA (version 1.4.1) were fit to the incidence data for selected end points in female rats and male and female mice exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a) (Table A-8). To provide potential points of departure for MRL derivation, 10% extra risk was selected as the benchmark response in accordance with U.S. EPA (2000) technical guidance for benchmark dose analysis to select a response level near the lower range of detectable observations. The BMD_{10s} and $BMDL_{10s}$ from the best fitting models for nonneoplastic lesions of the liver (female rats and mice), duodenum (male and female mice), mesenteric lymph nodes (male and female mice), and pancreas (female mice) are shown in Table A-9. For chronic inflammation of the liver in female rats, the log-logistic model provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.22 and 0.14 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in male mice, the multistage and quantal linear models provided the best fit, with BMD_{10} and $BMDL_{10}$ values of 0.16 and 0.13 mg chromium(VI)/kg/day, respectively. For diffuse epithelial hyperplasia in female mice, the best

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fit was provided by several models (gamma, multistage, quantal linear, and weibull) with BMD₁₀ and BMDL₁₀ values of 0.12 and 0.09 mg chromium(VI)/kg/day, respectively. For histiocytic alteration of the liver and cytoplasm alteration of the pancreas in female mice, the log-logistic model provided the best fit, with BMD₁₀ and BMDL₁₀ values of 0.17 and 0.12 mg chromium(VI)/kg/day, respectively, for liver lesions and of 0.68 and 0.52 mg chromium(VI)/kg/day, respectively, for pancreas lesions. For lesions of the mesenteric lymph nodes in male and female mice, none of the models provided adequate fit to the data, even with the two highest doses dropped from the analysis; thus, data sets for these lesions were considered not suitable for BMD analysis. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. Based on the lowest BMDL₁₀ value of 0.09 mg chromium(VI)/kg/day, diffuse epithelial hyperplasia of the duodenum in female mice was selected as the point of departure for derivation of the chronic-duration oral MRL. The chronic-duration oral MRL based on nonneoplastic lesions of the duodenum in female mice is expected to be protective for all other adverse effects observed in the 2-year drinking water study (e.g., hematological effects and lesions of the liver, lymph nodes, pancreas, and salivary gland). The chronic-duration MRL of 0.0009 mg chromium(VI)/kg/day was derived by dividing the BMDL₁₀ by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Table A-9. Summary of BMD₁₀ and BMDL₁₀ from the Best Fitting Models for Nonneoplastic Lesions of the Liver, Duodenum, Mesenteric Lymph Nodes, and Pancreas in Female Rats and Male and Female Mice After Exposure to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

End point	Species/sex	Model	Number of doses	BMD ^a (mg/kg/day)	BMDL ^a (mg/kg/day)
Liver, chronic inflammation	Rat/female	Log-logistic	5	0.22	0.14
Duodenum: diffuse epithelial hyperplasia	Mouse/male	1-Degree polynomial multistage/quantal linear	4	0.16	0.13
Mesenteric lymph node: histiocytic cellular infiltration ^b	Mouse/male	—	—	—	—
Duodenum: diffuse epithelial hyperplasia	Mouse/female	Gamma/Multistage/quantal linear/weibull	3	0.12	0.09
Mesenteric lymph node: histiocytic cellular infiltration ^b	Mouse/female	—	—	—	—
Liver: histiocytic cellular infiltration	Mouse/female	Log-logistic	5	0.17	0.12
Pancreas: acinus, cytoplasmic alteration	Mouse/female	Log-logistic	5	0.68	0.52

^aBMDs and BMDLs from dichotomous data are associated with a 10% extra risk; doses are in terms of mg chromium(VI)/kg/day.

^bNone of the models provided an adequate fit to the data.

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Uncertainty Factors used in MRL derivation:

- ☐ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Daily doses for each treatment group were reported by study authors (NTP 2008a) based on body weights and water intake over the 2-year exposure period.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Selection of nonneoplastic lesions of the duodenum in female mice is as the critical effect for the chronic-duration oral MRL is supported by observations from the same study showing adverse gastrointestinal effects in male mice (diffuse epithelial hyperplasia at ≥ 0.38 mg chromium(VI)/kg/day and histiocytic cellular infiltration at 5.9 mg chromium(VI)/kg/day) and in male and female rats (histiocytic cellular infiltration at ≥ 0.77 and ≥ 0.94 mg chromium(VI)/kg/day, respectively) exposed to sodium dichromate dihydrate in drinking water for 2 years (NTP 2008a). Although no other chronic-duration studies on oral chromium(VI) in animals were identified, a 3-month study on sodium dichromate dihydrate in drinking water revealed adverse gastrointestinal effects in rats and mice (including a comparative study in 3 mouse strains) (NTP 2007). Epithelial hyperplasia and histiocytic cellular infiltration of the duodenum was observed at ≥ 3.1 and ≥ 5.9 mg chromium(VI)/kg/day, respectively, in male and female B6C3F1 mice. Similar nonneoplastic lesions of the duodenum were also reported in the 3-month comparative study in male B6C3F1, BALB/c, and C57BL/6 mice, with epithelial hyperplasia at ≥ 2.8 mg chromium(VI)/kg/day in B6C3F1 and BALB/c strains and ≥ 5.2 in the C57BL/6 strain, and histiocytic cellular infiltration at ≥ 2.8 mg chromium(VI)/kg/day in B6C3F1 and C57BL/6 strains and ≥ 5.2 mg chromium(VI)/kg/day in the BALB/c strain. In male and female F344/N rats, histiocytic cellular infiltration was observed at ≥ 3.5 mg chromium(VI)/kg/day. At a higher daily dose (20.9 mg chromium(VI)/kg/day), ulcer, epithelial regenerative focal hyperplasia, and epithelial focal squamous metaplasia of the glandular stomach were observed.

Details of Benchmark Dose Analysis for the Chronic-duration Oral MRL

Chronic Inflammation of the Liver in Female Rats. As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit (X^2 p-value ≥ 0.1) to the data (Table A-10). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.22 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.14 mg chromium(VI)/kg/day (Figure A-4).

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Table A-10. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	χ^2 p-value	AIC
Gamma ^a	0.51	0.37	0.04	317.97
Logistic	0.84	0.65	0.01	321.45
Log-logistic^b	0.22	0.14	0.37	312.57
Multi-stage ^c	0.51	0.37	0.04	317.97
Probit	0.88	0.70	0.01	321.80
Log-probit ^b	0.89	0.61	0.01	320.86
Quantal linear	0.51	0.37	0.04	317.97
Weibull ^a	0.51	0.37	0.04	317.97

^aRestrict power ≥ 1

^bSlope restricted to >1

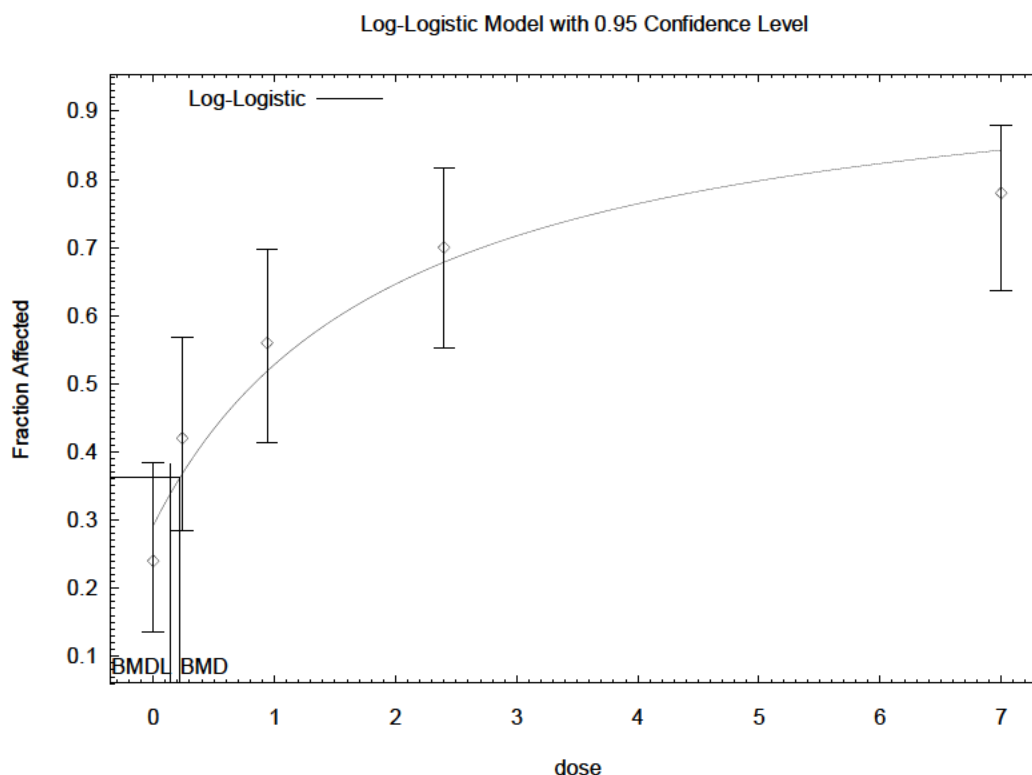
^cRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Figure A-4. Predicted and Observed Incidence of Chronic Inflammation of the Liver in Female Rats Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Diffuse Epithelial Hyperplasia of the Duodenum in Male Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-11). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, the gamma, log-logistic, multistage, log-probit, quantal linear, and weibull models provided adequate fits to the data (X^2 p-value > 0.1). Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the 1-degree polynomial multistage model provided the best fit to the data (Figure A-5). Based on the multistage model, the BMD associated with a 10% extra risk was 0.16 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.13 mg chromium(VI)/kg/day.

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Table A-11. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum in Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	χ^2 p-value	AIC
All doses				
Gamma ^a	0.31	0.25	0.00	270.99
Logistic	0.90	0.74	0.00	296.25
Log-logistic ^b	0.15	0.12	0.00	247.93
Multi-stage ^c	0.31	0.25	0.00	270.99
Probit	0.90	0.76	0.00	296.18
Log-probit ^b	0.48	0.36	0.00	274.38
Quantal linear	0.31	0.25	0.00	270.99
Weibull ^a	0.31	0.25	0.00	270.99
Highest dose dropped (four doses modeled)				
Gamma ^a	0.22	0.14	0.43	167.67
Logistic	0.47	0.39	0.03	177.09
Log-logistic ^b	0.26	0.15	0.20	169.23
Multi-stage ^d	0.16	0.13	0.52	166.34
Probit	0.45	0.37	0.04	176.19
Log-probit ^b	0.28	0.23	0.33	167.41
Quantal linear	0.16	0.13	0.52	166.34
Weibull ^a	0.22	0.14	0.47	167.50

^aRestrict power ≥ 1

^bSlope restricted to >1

^cRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

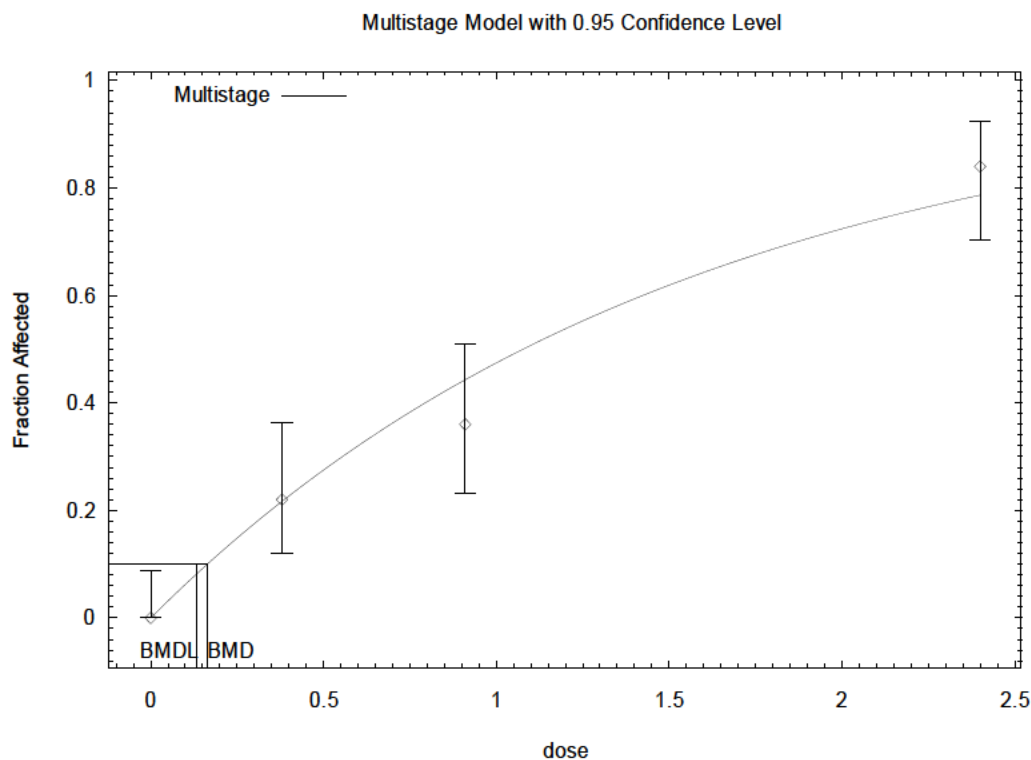
^dRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; degree polynomial =1.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Figure A-5. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



15:45 04/08 2008

*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Male Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-12). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is considered not suitable for benchmark dose modeling.

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Table A-12. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Male Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	χ^2 p-value	AIC
All doses				
Gamma ^a	0.38	0.26	0.00	285.94
Logistic	0.53	0.39	0.00	286.38
Log-logistic ^b	0.16	0.08	0.00	284.48
Multi-stage ^c	0.43	0.26	0.00	287.88
Probit	0.56	0.43	0.00	286.35
Log-probit ^b	0.83	0.52	0.00	289.36
Quantal linear	0.38	0.26	0.00	285.94
Weibull ^a	0.38	0.26	0.00	285.94
Highest dose dropped (four doses modeled)				
Gamma ^a	0.47	0.24	0.00	258.50
Logistic	0.61	0.35	0.00	259.04
Log-logistic ^b	0.21	0.08	0.00	256.81
Multi-stage ^d	0.47	0.24	0.00	258.50
Probit	0.63	0.37	0.00	259.08
Log-probit ^b	1.24	0.56	0.00	261.28
Quantal linear	0.47	0.24	0.00	258.50
Weibull ^a	0.47	0.24	0.00	258.50
Two highest doses dropped (three doses modeled)				
Gamma ^a	0.11	0.07	0.00	187.77
Logistic	0.17	0.12	0.00	189.97
Log-logistic ^b	0.05	0.03	0.00	183.77
Multi-stage ^e	0.11	0.07	0.00	187.77
Probit	0.17	0.12	0.00	190.12
Log-probit ^b	0.17	0.11	0.00	190.37
Quantal linear	0.11	0.07	0.00	187.77
Weibull ^a	0.11	0.07	0.00	187.77

^aRestrict power ≥ 1

^bSlope restricted to >1

^cRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

^dRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.

^eRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Diffuse Epithelial Hyperplasia of the Duodenum in Female Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the data (Table A-13). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. After dropping the highest dose, an adequate fit was still not achieved. After dropping the two highest doses, all of the models except for the logistic and probit models provided an adequate fit (X^2 p-value ≥ 0.1) to the data. Comparing across models, a better fit is generally indicated by a lower AIC (EPA 2000). As assessed by AIC, the gamma, multistage, quantal linear, and weibull models generated identical goodness of fit statistics and benchmark doses, as these models all took the form of a 1-degree polynomial multistage model which provides the best fit (Figure A-6). Based on these models, the BMD associated with a 10% extra risk was 0.12 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.09 mg chromium(VI)/kg/day.

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Table A-13. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	x ² p-value	AIC
All doses				
Gamma ^a	0.34	0.27	0.00	275.34
Logistic	0.88	0.72	0.00	293.17
Log-logistic ^b	0.12	0.09	0.04	245.54
Multi-stage ^c	0.34	0.27	0.00	275.34
Probit	0.93	0.78	0.00	294.03
Log-probit ^b	0.52	0.38	0.00	279.54
Quantal linear	0.34	0.27	0.00	275.34
Weibull ^a	0.34	0.27	0.00	275.34
Highest dose dropped (four doses modeled)				
Gamma ^a	0.20	0.16	0.00	213.41
Logistic	0.55	0.46	0.00	236.10
Log-logistic ^b	0.11	0.08	0.04	200.07
Multi-stage ^d	0.20	0.16	0.00	213.41
Probit	0.54	0.45	0.00	235.61
Log-probit ^b	0.29	0.24	0.00	220.04
Quantal linear	0.20	0.16	0.00	213.41
Weibull ^a	0.20	0.16	0.00	213.41
Two highest doses dropped (three doses modeled)				
Gamma^a	0.12	0.09	0.87	126.06
Logistic	0.34	0.27	0.00	141.77
Log-logistic ^b	0.12	0.06	1.00	127.77
Multi-stage^e	0.12	0.09	0.87	126.06
Probit	0.32	0.26	0.00	140.65
Log-probit ^b	0.20	0.16	0.48	127.17
Quantal linear	0.12	0.09	0.87	126.06
Weibull^a	0.12	0.09	0.87	126.06

^aRestrict power >=1

^bSlope restricted to >1

^cRestrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

^dRestrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.

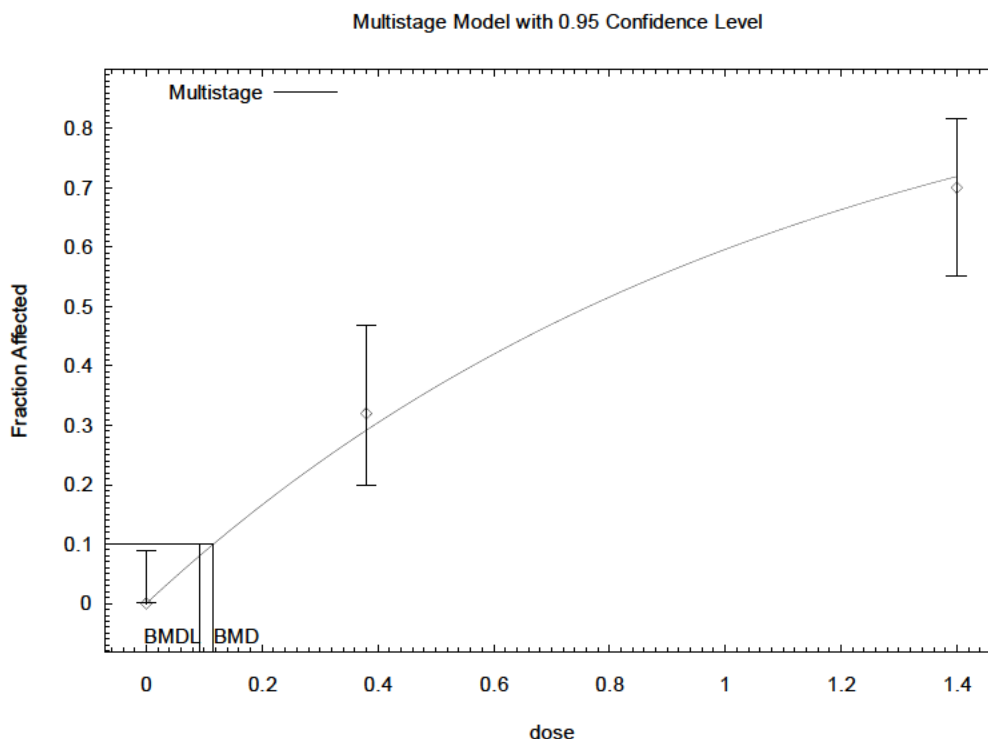
^eRestrict betas >=0; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Figure A-6. Predicted and Observed Incidence of Diffuse Epithelial Hyperplasia in the Duodenum of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



09:36 04/09 2008

*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Histiocytic Cellular Infiltration of the Mesenteric Lymph Nodes in Female Mice. As assessed by the chi-square goodness-of-fit statistic, none of the models provided an adequate fit (X^2 p-value ≥ 0.1) to the full dataset (Table A-14). In order to achieve a statistically fit model, the highest dose was dropped. This is determined to be appropriate, as the area of concern is with the low-dose region of the response curve. Dropping the highest dose did not result in adequately fitting models, nor did dropping the two highest doses. This dataset is not suitable for benchmark dose modeling.

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Table A-14. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in Mesenteric Lymph Nodes of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	χ^2 p-value	AIC
All doses				
Gamma ^a	0.41	0.30	0.00	282.46
Logistic	0.77	0.61	0.00	290.18
Log-logistic ^b	0.09	0.06	0.00	263.55
Multi-stage ^c	0.41	0.30	0.00	282.46
Probit	0.85	0.69	0.00	291.41
Log-probit ^b	0.68	0.47	0.00	285.85
Quantal linear	0.41	0.30	0.00	282.46
Weibull ^a	0.41	0.30	0.00	282.46
Highest dose dropped (four doses modeled)				
Gamma ^a	0.20	0.15	0.00	224.84
Logistic	0.40	0.33	0.00	230.81
Log-logistic ^b	0.07	0.05	0.00	215.19
Multi-stage ^d	0.20	0.15	0.00	224.84
Probit	0.40	0.34	0.00	230.85
Log-probit ^b	0.37	0.24	0.00	231.76
Quantal linear	0.20	0.15	0.00	224.84
Weibull ^a	0.20	0.15	0.00	224.84
Two highest doses dropped (three doses modeled)				
Gamma ^a	0.14	0.10	0.00	172.32
Logistic	0.31	0.24	0.00	178.99
Log-logistic ^b	0.07	0.04	0.00	164.47
Multi-stage ^e	0.14	0.10	0.00	172.32
Probit	0.30	0.23	0.00	178.74
Log-probit ^b	0.21	0.15	0.00	178.11
Quantal linear	0.14	0.10	0.00	172.32
Weibull ^a	0.14	0.10	0.00	172.32

^aRestrict power ≥ 1

^bSlope restricted to >1

^cRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

^dRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 2-degree polynomial is reported.

^eRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Histiocytic Cellular Infiltration of the Liver in Female Mice. As assessed by the chi-square goodness-of-fit statistic, only the log-logistic model provided an adequate fit (X^2 p-value ≥ 0.1) to the data (Table A-15). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.17 mg chromium(VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.12 mg chromium(VI)/kg/day (Figure A-7).

Table A-15. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Histiocytic Cellular Infiltration in the Liver of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	χ^2 p-value	AIC
Gamma ^a	0.35	0.28	0.08	255.40
Logistic	0.85	0.70	0.00	267.56
Log-logistic^b	0.17	0.12	0.44	251.36
Multi-stage ^c	0.35	0.28	0.08	255.40
Probit	0.88	0.75	0.00	268.64
Log-probit ^b	0.62	0.48	0.01	260.00
Quantal linear	0.35	0.28	0.08	255.40
Weibull ^a	0.35	0.28	0.08	255.40

^aRestrict power ≥ 1

^bSlope restricted to >1

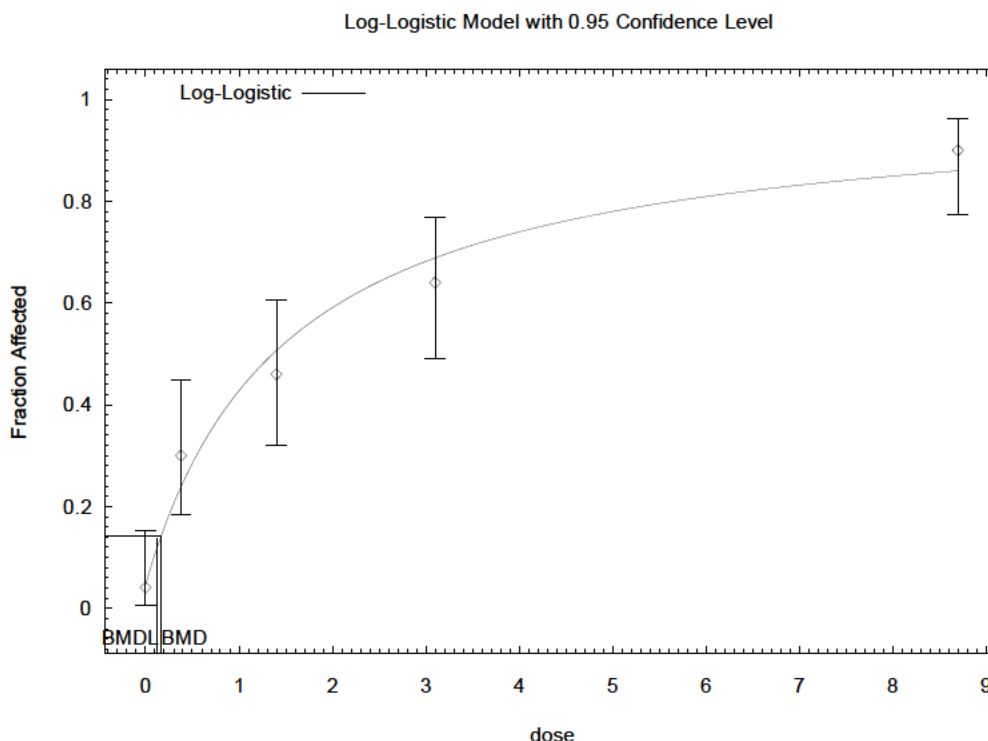
^cRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; no degree of polynomial provided a fit, a 3-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Figure A-7. Predicted and Observed Incidence of Histiocytic Cellular Infiltration in the Livers of Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



11:17 04/09 2008

*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium(VI)/kg/day.

Source: NTP 2008a

Cytoplasmic Alteration of Acinar Epithelial Cells of the Pancreas in Female Mice. As assessed by the chi-square goodness-of-fit statistic, all of the models provide adequate fits (X^2 p-value ≥ 0.1) to the data (Table A-16). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC) (EPA 2000). As assessed by AIC, the log-logistic model provides the best fit (Figure A-8). Based on the log-logistic model, the BMD associated with a 10% extra risk was 0.68 mg chromium (VI)/kg/day and its lower 95% confidence limit (BMDL) was 0.52 mg chromium (VI)/kg/day.

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Table A-16. BMD₁₀ and BMDL₁₀ Values and Goodness-of-Fit Statistics from Models Fit to Incidence Data for Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	χ^2 p-value	AIC
Gamma ^a	0.92	0.72	0.13	206.82
Logistic	2.43	2.03	0.09	211.78
Log-logistic^b	0.68	0.52	0.19	205.22
Multi-stage ^c	0.92	0.72	0.13	206.82
Probit	2.24	1.89	0.11	210.99
Log-probit ^b	1.77	1.40	0.11	209.99
Quantal linear	0.92	0.72	0.13	206.82
Weibull ^a	0.92	0.72	0.13	206.82

^aRestrict power ≥ 1

^bSlope restricted to >1

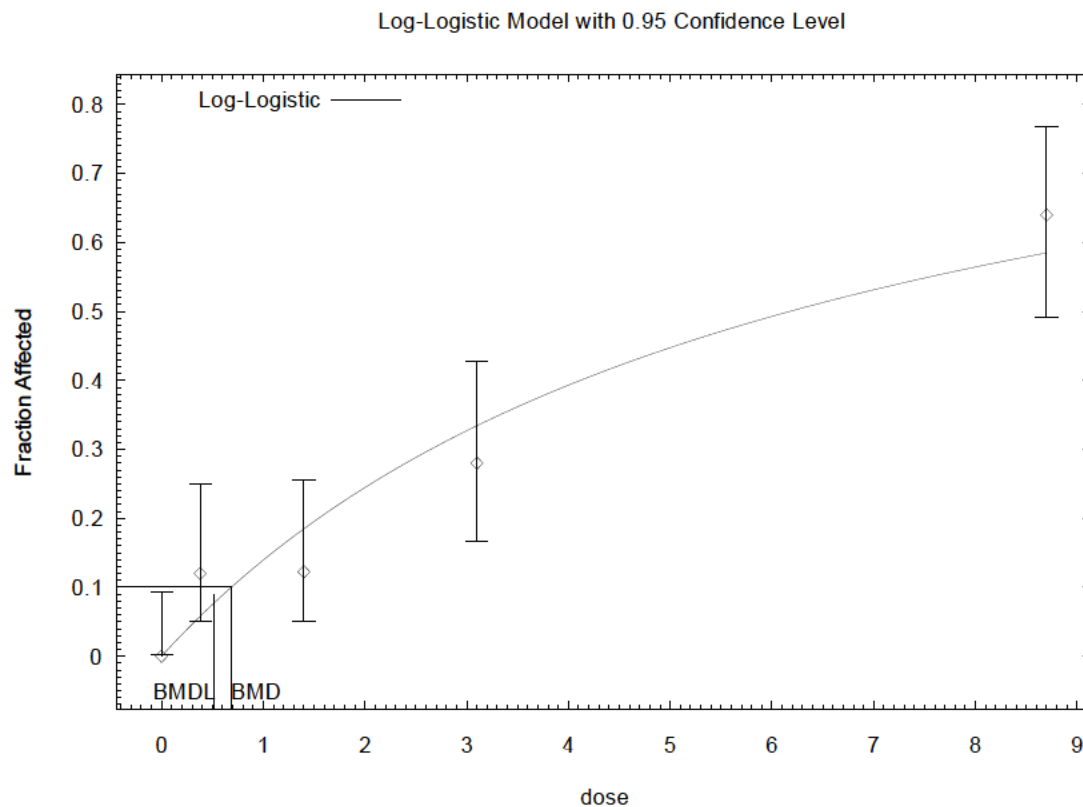
^cRestrict betas ≥ 0 ; lowest degree polynomial (up to n-2) with an adequate fit is reported; a 1-degree polynomial is reported.

AIC = Akaike information criterion; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2008a

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Figure A-8. Predicted and Observed Incidence of Pancreas: Acinus, Cytoplasmic Alteration in Female Mice Exposed to Sodium Dichromium Dihydrate in Drinking Water for 2 Years*



11:41 04/09 2008

*BMDs and BMDLs indicated are associated with a 10% extra risk, and are in units of mg chromium (VI)/kg/day.

Source: NTP 2008a

Agency Contact (Chemical Manager): Sharon Wilbur

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(III) insoluble particulates
CAS number: 16065-83-1
Date: February 2012
Profile status: Second Draft Post-Public Comment
Route: ☒ Inhalation ☐ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Key to figure: 2
Species: Rat

Minimal Risk Level: 0.005 mg chromium(III)/m³ for insoluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m³ (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m³ groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly, but food consumption was not measured. Ophthalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β₂-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m³ groups. For all animals in the 3 and 30 mg chromium(III)/m³ groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological lesions were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to chromic oxide only; detailed results of animals exposed to basic chromium sulfate are presented in the following intermediate-duration inhalation MRL worksheet for soluble chromium(III) compounds. No mortalities, clinical signs of toxicity, changes in body weight, findings on ophthalmologic examination, or alterations of sperm count, motility, or morphology were observed. Evaluations of hematology, clinical chemistry, and urinalysis did not reveal any treatment-related differences compared to controls; β₂-microglobulin was not detected in urine of rats from any group. Absolute and relative lung/trachea weights were significantly increased by 12 and 13%, respectively, in males in the 30 mg

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chromium(III)/m³ group compared to control. Lung weights were not increased in females. Other significant changes in organ weight changes were limited to small increases in absolute thyroid/parathyroid weight in females in the 10 mg chromium(III)/m³ group and in relative thyroid/parathyroid weight (combined) in females in the 10 and 30 mg chromium(III)/m³ groups. The study authors stated that the biological significance of changes in thyroid/parathyroid weight could not be determined; however, no histopathological changes were observed in these tissues in female rats exposed to 30 mg chromium(III)/m³. On necropsy, most animals (incidence not reported) in the chromic oxide group had green discoloration of the lungs and mediastinal lymph nodes; the degree of discoloration increased with exposure level and was presumed to represent deposition of the test material. Mediastinal lymph node enlargement was noted in the 30 mg chromium(III)/m³ group. Microscopic examination of the lung revealed foci or aggregates of dark-pigmented (presumably the test material) macrophages within alveolar spaces adjacent to junctions of terminal bronchioles and alveolar ducts; black pigment was observed at the tracheal bifurcation and in periobronchial lymphoid tissue and the mediastinal lymph node in all chromic oxide treatment groups. These findings are consistent with normal physiological clearance mechanisms for particulates deposited in the lung and are not considered adverse. Lymphoid hyperplasia of the mediastinal node was observed in rats of all treatment groups (severity not reported). In rats exposed to 10 and 30 mg chromium(III)/m³, trace-to-mild chronic interstitial inflammation of the lung, characterized by inflammatory cell infiltration, was observed in alveolar septa, and hyperplasia of Type II pneumocytes (severity not reported) were observed. Histopathological changes were isolated to the lungs and respiratory lymphatic tissues and were not observed in other tissues, including nasal tissues and the larynx. Thus, for evaluations conducted at the end of the 13-week treatment period, a LOAEL of 3 mg chromium(III)/m³ for hyperplasia of the mediastinal node was identified for both males and females; the severity of this effect was not reported. Following the 13-week recovery period, pigmented macrophages and black pigment were observed in peribronchial tissues and the mediastinal lymph node in animals from all treatment groups. Septal cell hyperplasia and chronic interstitial inflammation of the lung, both trace-to-mild in severity, were observed in males of all treatment groups and in females exposed to 10 and 30 mg chromium(III)/m³. For evaluations conducted at the 13-week posttreatment recovery period, a minimal LOAEL (classified as minimal based on severity) of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was identified.

Dose end point used for MRL derivation: 3 mg chromium(III)/m³ (trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung), adjusted to 0.54 mg chromium(III)/m³ for intermittent exposure and converted to a LOAEL_{HEC} of 0.43 mg chromium(III)/m³

[] NOAEL [X] LOAEL

The LOAEL of 3 mg chromium(III)/m³ for hyperplasia of the mediastinal node in males and females (observed at the end of the 13-week treatment period) and the minimal LOAEL (based on severity) of 3 mg chromium(III)/m³ for trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in males (observed at the end of the 13-week recovery period) were further evaluated as potential critical effects for derivation of the intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds. A BMCL for these effects could not be determined since incidence data for lesions of the lung and respiratory lymphatic tissue were not reported; thus, a NOAEL/LOAEL approach was used. Following adjustment of LOAELs for intermittent exposure (LOAEL_{ADI}) and human equivalent concentrations (LOAEL_{HEC}), as described below, trace-to-mild septal cell hyperplasia and chronic interstitial inflammation of the lung in male rats was selected as the critical effect, based on the lowest LOAEL_{HEC} of 0.43 mg chromium(III)/m³ (Table A-17). The intermediate-duration inhalation MRL for insoluble trivalent chromium particulate compounds of 0.005 mg chromium(III)/m³ was derived by dividing the minimal LOAEL_{HEC} of 0.43 mg chromium(III)/m³ by a composite uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Table A-17. LOAEL Values (Expressed in Terms Of HEC) for Nonneoplastic Lesions in Rats Exposed to Chromic Oxide by Inhalation For 13 Weeks

Species/sex	Lesion type (RDDR location)	RDDR multiplier	LOAEL _{ADJ} (mg chromium(III)/m ³) ^a	LOAEL _{HEC} (mg chromium(III)/m ³) ^b
Rat/male	Septal cell hyperplasia and chronic interstitial inflammation of the lung (thoracic)	0.789	0.54	0.43
Rat/male	Hyperplasia of the mediastinal node (tracheobronchial)	1.225	0.54	0.66
Rat/female	Hyperplasia of the mediastinal node (tracheobronchial)	1.084	0.54	0.59

^aDuration-adjusted for intermittent exposure (LOAEL_{ADJ} = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m³ x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m³)

^bLOAEL_{HEC} = LOAEL_{ADJ} x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL

[X] 3 for extrapolation from animals to humans, with dosimetric adjustment

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine the LOAEL_{HEC}, the LOAEL_{ADJ} in rats was multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract in male and female rats (Table A-17). The RDDR computer program was used to determine the RDDR multipliers as follows.

For interstitial inflammation of the lung in male rats (specific location of lesion within the lung was not reported by study authors) observed after the 13-week recovery period, the thoracic region for the RDDR program was selected since the observed effect could occur in the both the tracheobronchial and pulmonary regions of the lung. The RDDR multiplier of 0.789 for the thoracic region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size (MMAD±GSD) of 1.9±1.85 reported in the Derelanko et al. (1999) study.

For hyperplasia of the mediastinal node in male and female rats observed at the end of the 13-week treatment period, the tracheobronchial region of the respiratory tract was selected for the RDDR program. Although the mediastinal lymph node is not a respiratory tissue, for the purposes of HEC conversions, it is considered part of the tracheobronchial region of the respiratory system rather than a systemic tissue;

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classification of the mediastinal lymph node as a systemic tissue is not appropriate, since the test material reaches the respiratory lymphatic tissues by the pulmonary macrophage clearance system and not by first entering the systemic circulation. For male rats, the RDDR multiplier of 1.225 for the tracheobronchial region of the respiratory tract in male rats was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study (data for body weights of male rats in the chromic oxide portion of the study were not reported) and the average particle size $\text{MMAD} \pm \text{GSD}$ of 1.9 ± 1.85 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 1.084 for the tracheobronchial region tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size $\text{MMAD} \pm \text{GSD}$ of 1.9 ± 1.85 reported in the Derelanko et al. (1999) study; the default value for female body weights was used because female body weights were not reported in the critical study.

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks.

$$\text{LOAEL}_{\text{ADJ}} = 3 \text{ mg chromium(III)}/\text{m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$

$$\text{LOAEL}_{\text{ADJ}} = 0.54 \text{ mg chromium(III)}/\text{m}^3$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Agency Contact (Chemical Manager): Sharon Wilbur

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Chromium(III) soluble particulates
CAS number: 16065-83-1
Date: June 2012
Profile status: Third Draft Post-Public Comment
Route: ☒ Inhalation ☐ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Key to figure: 3
Species: Rat

Minimal Risk Level: 0.0001 mg chromium(III)/m³ for soluble trivalent chromium particulate compounds

Reference: Derelanko MJ, Rinehart WE, Hilaski RJ, et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic acid and basic chromium sulfate. Toxicol Sci 52(2):278-288.

Experimental design: Groups of 15 male and female CDF (Fisher 344/Crl BR VAF/Plus) rats were exposed to chromic oxide or basic chromium sulfate by nose-only inhalation to 0, 3, 10, or 30 mg chromium(III)/m³ (measured concentrations) 6 hours/day, 5 days/week for 13 weeks. Mean particle sizes (in microns±GSD, based on 21 samples/test group evaluated over the 13-week exposure period) in the 3, 10, and 30 mg chromium(III)/m³ groups, were 1.8±1.93, 1.9±1.84, and 1.9±1.78, respectively, for chromic oxide and 4.2±2.48, 4.2±2.37, and 4.5±2.50, respectively, for basic chromium sulfate; no chromium(VI) was detected in samples. Of these 15 rats/sex/group, 10 rats/sex/group were examined and sacrificed after 13 weeks of exposure and 5 rats/sex/group were examined and sacrificed after an additional 13-week recovery (e.g., no exposure) period. Throughout the exposure and recovery periods, rats were examined daily for mortality and clinical signs of toxicity; body weight was recorded weekly but food consumption was not measured. Ophthalmoscopic examinations were conducted prior to treatment and before terminal sacrifice. At the end of the treatment and recovery phases, blood was analyzed for "standard" hematology and clinical chemistry, and urinalysis was conducted; specific outcome measures evaluated for these assessments were not reported. In five rats/sex/group, urine was also analyzed for β₂-microglobulin. Gross necropsy was performed on all animals at terminal sacrifice and organ weights were recorded for heart, liver, lungs/trachea (combined), spleen, kidneys, brain, adrenal, thyroid/parathyroid, testes, and ovaries. Bone marrow was examined and differential cell counts of bone marrow were conducted. Microscopic examination of comprehensive tissues (described as "tissues typically harvested for subchronic studies") was conducted for all animals and the control and 30 mg chromium(III)/m³ groups. For all animals in the 3 and 30 mg chromium(III)/m³ groups, the following tissues were examined microscopically: kidneys, liver, nasal tissues, trachea, lungs, larynx, mediastinal and mandibular lymph nodes, and all tissues with gross lesions. Histopathological findings were described, but no incidence data were reported. Sperm morphology, count, and motility were assessed in all males at the end of the 13-week treatment period only.

Effects noted in study and corresponding doses: The following study results are for rats exposed to basic chromium sulfate only; detailed results of animals exposed to chromic oxide are presented in the preceding intermediate-duration inhalation MRL worksheet for insoluble chromium(III) compounds. No treatment-related mortalities were observed; one male rat in the 30 mg chromium(III)/m³ group died on day 4 of exposure; the study authors did not attribute this death to treatment since no significant signs of toxicity were observed in this animals or in other animals in this treatment group. Females in the 30 mg chromium(III)/m³ group exhibited sporadic labored breathing; no additional information on this observation was reported. No findings on ophthalmologic examination or alterations of sperm count, motility, or morphology were observed. At the end of the 13-week treatment period, body weight was

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significantly decreased in males in the 10 and 30 mg chromium(III)/m³ groups and females in the 30 mg chromium(III)/m³ group. The study authors stated that “most” hematological, clinical chemistry, and urinalysis values in all exposure groups were similar to controls, although data were not reported. A significant, dose-related increase in absolute and relative lung/trachea weights was observed in male rats in all treatment groups. Other organ weight changes in males were decreased absolute and increase relative brain weights (30 mg chromium(III)/m³), increased relative kidney weight (30 mg chromium(III)/m³), decreased absolute liver weight (30 mg chromium(III)/m³), increased relative thyroid/parathyroid weight (30 mg chromium(III)/m³), decreased relative spleen weight (10 and 30 mg chromium(III)/m³), and increased relative testes weight (30 mg chromium(III)/m³). In females, absolute and relative lungs weights were increased in a dose-dependent fashion in all treatment groups. Other organ weight changes in females were increased absolute and relative thyroid/parathyroid weight (30 mg chromium(III)/m³) and decreased absolute spleen weight (30 mg chromium(III)/m³). With the exception of increased absolute and relative lung weights in males and females, small changes in other organs weights were not considered adverse in the absence of histopathological changes. On necropsy, grey lung discoloration was observed in animals exposed to 10 and 30 mg chromium(III)/m³; the degree of discoloration increased with exposure level. Microscopic examination of the lung revealed the following changes in all treatment groups: chronic inflammation of the alveoli; alveolar spaces filled with macrophages, neutrophils, lymphocytes and cellular debris; foci of “intense” inflammation and thickened alveolar walls; chronic interstitial inflammation with cell infiltration; hyperplasia of Type II pneumocytes; and granulomatous inflammation, characterized by infiltration of macrophages and multinucleated giant cells. Macrophage infiltration and granulomatous inflammation of the larynx, acute inflammation and suppurative and mucoid exudates of nasal tissues, and histiocytosis and hyperplasia of peribronchial lymphoid tissues and the mediastinal lymph node were also observed in all treatment groups. Following the 13-week recovery period, enlargement of the mediastinal lymph node was observed on gross necropsy in all treatment groups. Microscopic examination of respiratory tissues showed changes to the lung (chronic alveolar inflammation, interstitial inflammation, septal cell hyperplasia, and granulomatous inflammation) in all treatment groups, larynx (granulomatous inflammation) in the 10 and 30 mg chromium(III)/m³ groups, nasal tissues (trace suppurative exudates) in one to two animals in each groups, and mediastinal lymph node (histiocytosis and hyperplasia) in all treatment groups chromium(III)/m³ groups. Following the 13-week recovery period, test material was observed in the respiratory tract on necropsy; however, incidence was decreased compared to observations made immediately following treatment (data not presented). In addition, chronic alveolar and interstitial inflammation and septal cell hyperplasia (all trace-to-moderate in severity) were observed in the 10 and 30 mg chromium(III)/m³ groups, with severity similar to that observed immediately following treatment; in the 3 mg chromium(III)/m³ group, severity was slightly reduced.

Dose end point used for MRL derivation: 3 mg chromium(III)/m³ (nasal and larynx lesions), adjusted to 0.54 mg chromium(III)/m³ for intermittent exposure and converted to a LOAEL_{HEC} of 0.04 mg chromium(III)/m³

[] NOAEL [X] LOAEL

The respiratory tract was identified as the target for inhaled soluble trivalent chromium particulate compounds. Similar effects were observed in male and female rats exposed to inhaled basic chromium sulfate for 13 weeks, with histopathological changes to the nose, larynx, lung, and respiratory lymphatic tissues and increased relative lung weight occurring at ≥3 mg chromium(III)/m³. Therefore, data for histopathological changes in various regions of the respiratory tract and increased relative lung weights were further evaluated to determine the point of departure for derivation of the intermediate-duration MRL for soluble trivalent chromium particulate compounds.

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Benchmark dose analysis could not be conducted for respiratory tract lesions, since incidence data were not reported by Derelanko et al. (1999); therefore, a NOAEL/LOAEL approach was used. The LOAEL value of 3 mg chromium(III)/m³ for lesions in different regions of the respiratory tract was further evaluated as a potential point of departure. LOAEL values were adjusted for intermittent exposure (LOAEL_{ADJ}) and converted to a human equivalent concentration (LOAEL_{HEC}), as shown in (Table A-18).

Table A-18. LOAEL Values (Expressed in Terms of HEC) for Nonneoplastic Lesions in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Species/sex	Lesion type (RDDR location)	RDDR multiplier	LOAEL _{ADJ} (mg chromium(III)/m ³) ^a	LOAEL _{HEC} (mg chromium(III)/m ³) ^b
Rat/male	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.129	0.54	0.07
Rat/male	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.470	0.54	0.25
Rat/female	Granulomatous inflammation of larynx; inflammation of nasal tissue (extrathoracic)	0.078	0.54	0.04
Rat/female	Interstitial and alveolar inflammation; alveolar hyperplasia (thoracic)	0.483	0.54	0.26

^aDuration-adjusted for intermittent exposure (LOAEL_{ADJ} = LOAEL x 6 hours/24 hours x 5 days/7 days = 3 mg chromium(III)/m³ x 6 hours/24 hours x 5 days/7 days = 0.54 mg chromium(III)/m³)

^bLOAEL_{HEC} = LOAEL_{ADJ} x RDDR

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

To determine the BMC for increased lung weights, available continuous-variable models in the EPA Benchmark Dose (version 1.4.1) were fit to the data for relative lung weights in male and female rats (Derelanko et al. 1999; Table A-19). The BMC and the 95% lower confidence limit (BMCL) calculated is an estimate of the concentrations associated with a change of 1 standard deviation from the control (BMCL_{1sd}). The model-fitting procedure for continuous data is as follows. The simplest model (linear) is applied to the data while assuming constant variance. If the data are consistent with the assumption of

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constant variance ($p \geq 0.1$), then the other continuous models (polynomial, power, and Hill models) are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest Akaike's Information Criteria (AIC) for the fitted model is selected for BMC derivation. If the test for constant variance is negative, then the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the other continuous models are applied to the data. Among the models providing adequate fits to the means ($p \geq 0.1$), the one with the lowest AIC for the fitted model is selected for BMC derivation. If the tests for both constant and nonconstant variance are negative, then the data set is considered not to be suitable for BMC modeling. For male rats, the best model fit (Hill model) did not provide graphic output of the model; since model fit could not be evaluated by visual inspection, the $BMDL_{1sd}$ from the Hill model was not selected. All other models took the form of a linear model (nonconstant variance), yielding predicted BMC_{1sd} and $BMCL_{1sd}$ values of 2.89 and 2.05 mg chromium(III)/ m^3 , respectively. For female rats, the linear model (nonconstant variance) provided the best fit, with predicted BMC_{1sd} and $BMCL_{1sd}$ values of 6.33 and 3.96 mg/ m^3 , respectively. Additional details of the benchmark dose analysis for each data set modeled are presented in the last section of this worksheet. The $BMCL_{1sd}$ values for the best fitting models in male and female rats were adjusted for intermittent exposure ($BMCL_{1sd, ADI}$) and human equivalent concentrations ($BMCL_{1sd, HEC}$), yielding $BMCL_{1sd, HEC}$ values of 0.17 and 0.34 mg chromium(III)/ m^3 in males and females, respectively, as shown below (Table A-20).

Table A-19. Relative Lung Weights^a of CDF Rats^b Exposed to Basic Chromium Sulfate by Nose-Only Inhalation 6 Hours/Day, 5 Days/Week for 13 Weeks

Relative weight (percent x 10)	Concentrations (mg chromium(III)/ m^3)			
	0	3	10	30
Basic chromium sulfate, males	4.42±0.187 ^c	5.60±0.271 ^d	7.1 5± 0.252 ^d	10.69±0.688 ^d
Basic chromium sulfate, females	5.65±0.418	6.99±0.619 ^d	9.24±1.036 ^d	12.89±1.134 ^d

^aCombined lung and trachea

^b10 rat in all groups except male rats in the basic chromium sulfate 30 mg/ m^3 group (n=9)

^cmean±Standard deviation

^dp<0.01

Source: Derelanko et al. 1999

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Table A-20. BMCL_{1sd} Values (Expressed in Terms of HEC) for Increased Relative Lung Weight in Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Species/sex	RDDR multiplier ^a	Duration-adjusted BMCL _{1sd, ADJ} (mg chromium(III)/m ³) ^b	BMCL _{1sd, HEC} (mg chromium(III)/m ³) ^c
Rat/male	0.470	0.37	0.17
Rat/female	0.483	0.71	0.34

^aFor thoracic region

^bDuration-adjusted for continuous exposure (BMCL_{1sd, ADJ} = BMCL_{1sd} x 6 hours/24 hours x 5 days/7 days); BMCL_{1sd} for the best fitting models for male and female rats were 2.05 and 3.96 mg chromium(III)/m³, respectively.

^cBMCL_{1sd, HEC} = BMCL_{1sd, ADJ} x RDDR

BMCL = lower confidence limit (95%) on the benchmark concentration; HEC = human equivalent concentration; RDDR = regional deposited dose ratio

Source: Derelanko et al. 1999

Based on comparison of LOAEL_{HEC} values for respiratory tract lesions and BMCL_{1sd, HEC} values for increased lung weight, the lowest value of 0.04 mg chromium(III)/m³ (the LOAEL_{HEC} for lesions of the larynx and nose in female rats) was selected as the point of departure. The intermediate-duration inhalation MRL for soluble trivalent chromium particulate compounds of 0.0001 mg chromium(III)/m³ was derived by dividing the LOAEL_{HEC} of 0.04 mg chromium(III)/m³ by a composite uncertainty factor of 300 (10 for use of a LOAEL, 3 for pharmacodynamic variability between animals to humans, and 10 for human variability).

Uncertainty factors used in MRL derivation:

[X] 10 for use of a LOAEL

[X] 3 for extrapolation from animals to humans

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: To determine human equivalent concentrations, LOAEL_{ADJ} values for lesions in various areas of the respiratory tract (Table A-18) and BMCL_{1sd, ADJ} values for changes in lung weights (Table A-20) were multiplied by the RDDR multiplier determined for lesions in various areas of the respiratory tract as follows.

For histopathological changes to the nose and larynx, the extrathoracic region for the RDDR program was selected. For male rats, the RDDR multiplier of 0.129 for the extrathoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.078 for the extrathoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

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For histopathological changes to the lung and increased relative lung weight, the thoracic region (a combination of tracheobronchial and pulmonary regions) was selected. For male rats, the RDDR multiplier of 0.470 for the thoracic region of the respiratory tract was determined using the average body weight of 201 g for male rats in the control group in the basic chromium sulfate portion of the study and the average particle size (MMAD±GSD) of 4.3±2.45 reported in Derelanko et al. (1999). For female rats, the RDDR multiplier of 0.483 for the thoracic region of the respiratory tract was determined using the default subchronic body weight of 124 g for female F344 rats (EPA 1988d) and the average particle size MMAD±GSD of 4.3±2.45 reported in Derelanko et al. (1999); the default value for female body weights was used because female body weights were not reported in Derelanko et al. (1999).

Was a conversion used from intermittent to continuous exposure? Rats were exposed for 6 hours/day, 5 days/week for 13 weeks. The LOAEL and BMCL_{1sd} values were adjusted for continuous exposure as follows:

$$\text{LOAEL}_{\text{ADJ}} \text{ or } \text{BMCL}_{1\text{sd}, \text{ADJ}} = \text{LOAEL or BMCL}_{1\text{sd}} \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the major target of inhalation exposure to chromium(III) and chromium(VI) compounds in humans and animals. Respiratory effects due to inhalation exposure are probably due to direct action of chromium at the site of contact. The available occupational studies for exposure to chromium(III) compounds include, or likely include, concomitant exposure to chromium(VI) compounds and other compounds that may produce respiratory effects (Langård 1980; Mancuso 1951; Osim et al. 1999). Thus, while the available data in humans suggest that respiratory effects occur following inhalation exposure to chromium(III) compounds, the respiratory effects of inhaled chromium(VI) and other compounds are confounding factors. Studies evaluating respiratory effects of intermediate-duration inhalation exposure of animals are limited to the critical study evaluating 13-week exposure to chromic oxide or basic chromium sulfate (Derelanko et al. 1999). Results of this study show that intermediate-duration inhalation exposure to chromic oxide or basic chromium sulfate produced adverse respiratory effects, as indicated by histopathological changes and increased lung weight. However, effects of chromic oxide were less severe and isolated to the lung and respiratory lymph tissues, whereas the effects of basic chromium sulfate were more severe and observed throughout the respiratory tract (e.g., nose, larynx, lung and respiratory lymph tissues). The authors suggest that differences in the respiratory toxicity of these compounds may be due to differences in chemical-physical properties (e.g., solubility, acidity). Based on the differences in respiratory toxicity between insoluble chromic oxide and soluble basic chromium sulfate, separate intermediate-duration inhalation MRLs were derived for insoluble and soluble trivalent chromium particulate compounds.

Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL for Soluble Trivalent Chromium Particulates

Lung Weights in Male Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMCs to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assessed by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-21). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the Hill model provides the best fit to the data; however, the BMDS software did not generate the graph output needed to assess visual fit of the model to the data. All other models took the form of a linear model, so the

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nonconstant variance-linear model is selected for BMC derivation. The predicted BMC_{1sd} and $BMCL_{1sd}$ for the data are 2.89 and 2.05 mg chromium(III)/m³, respectively (Figure A-9).

Table A-21. Model Predictions for Changes in Relative Lung Weights of Male CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Model	Variance p-value ^a	p-Value for the means ^a	AIC	BMC_{1sd} (mg chromium(III)/m ³)	$BMCL_{1sd}$ (mg chromium(III)/m ³)
Linear ^{b,c}	0.00	0.30	56.75	5.79	4.70
Linear^{c,d}	0.40	0.10	44.09	2.89	2.05
Polynomial (1-degree) ^{c,d}	0.40	0.10	44.09	2.89	2.05
Polynomial (2-degree) ^{c,d}	0.40	0.10	44.09	2.89	2.05
Polynomial (3-degree) ^{c,d}	0.40	0.10	44.09	2.89	2.05
Power ^d	0.40	0.10	44.09	2.89	2.05
Hill ^d	0.40	0.26	42.79	1.74	1.07

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bConstant variance assumed

^cRestriction = non-negative

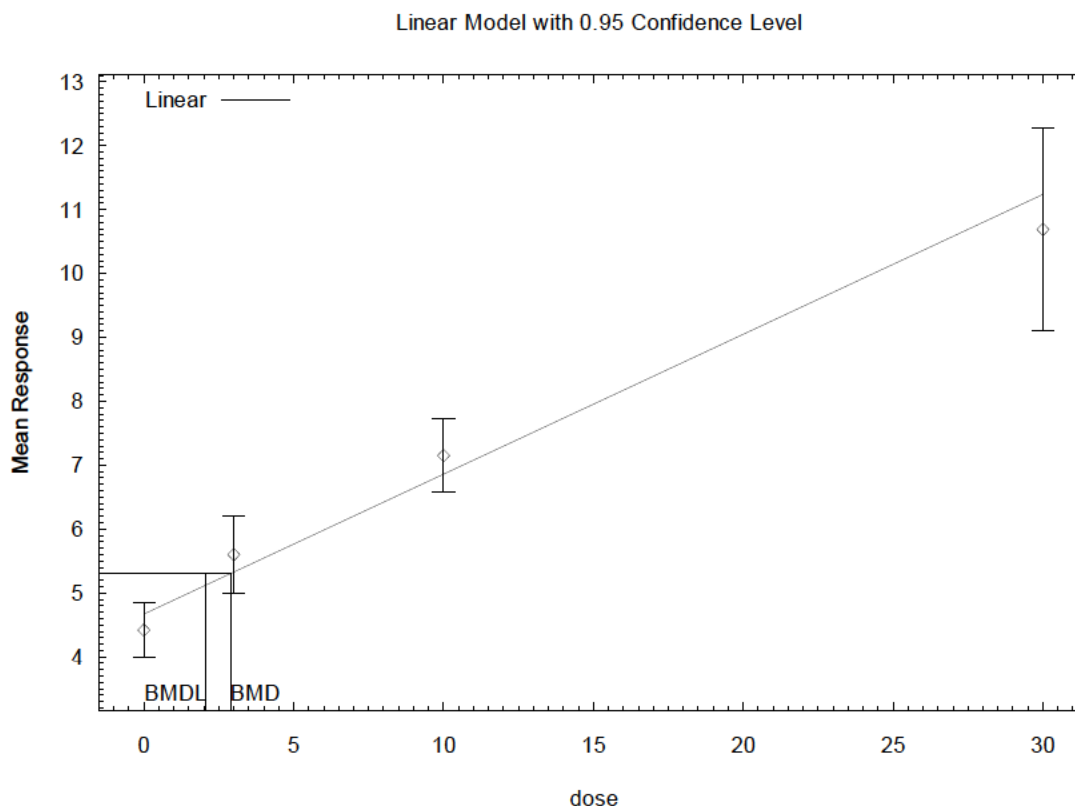
^dNonconstant variance model applied

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

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Figure A-9. Predicted and Observed Changes in Relative Lung Weights in Male Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks*



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*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m³.

Source: Derelanko et al. 1999

Lung Weights in Female Rats. The simplest model (linear) was applied to the data first to test for a fit for constant variance. The constant variance model did not provide an adequate fit (as assessed by the p-value for variance) to the data. The linear model was applied to the data again while applying the power model integrated into the BMDS to account for nonhomogenous variance. The nonconstant variance model did provide an adequate fit (as assessed by the p-value for variance). The polynomial, power, and Hill models were then fit to the data with nonconstant variance assumed. All of the models provided an adequate fit to the data (as assessed by the p-value for the means) (Table A-22). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the linear model provides the best fit to the data. The predicted BMC_{1sd} and BMCL_{1sd} for the data are 6.33 and 3.96 mg chromium(III)/m³, respectively (Figure A-10).

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Table A-22. Model Predictions for Changes in Relative Lung Weights of Female CDF Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks

Model	Variance p-value ^a	p-Value for the means ^a	AIC	BMC _{1sd} (mg chromium(III)/m ³)	BMCL _{1sd} (mg chromium(III)/m ³)
Linear ^{b,c}	0.01	0.51	122.61	11.28	8.59
Linear^{c,d}	0.59	0.14	117.05	6.33	3.96
Polynomial (1-degree) ^{c,d}	0.59	0.14	117.05	6.33	3.96
Polynomial (2-degree) ^{c,d}	0.59	0.14	117.05	6.33	3.96
Polynomial (3-degree) ^{c,d}	0.59	0.14	117.05	6.33	3.96
Power ^d	0.59	0.14	117.05	6.33	3.96
Hill ^d	0.59	NA ^e	117.13	2.84	1.32

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bConstant variance assumed

^cRestriction = non-negative

^dNonconstant variance model applied

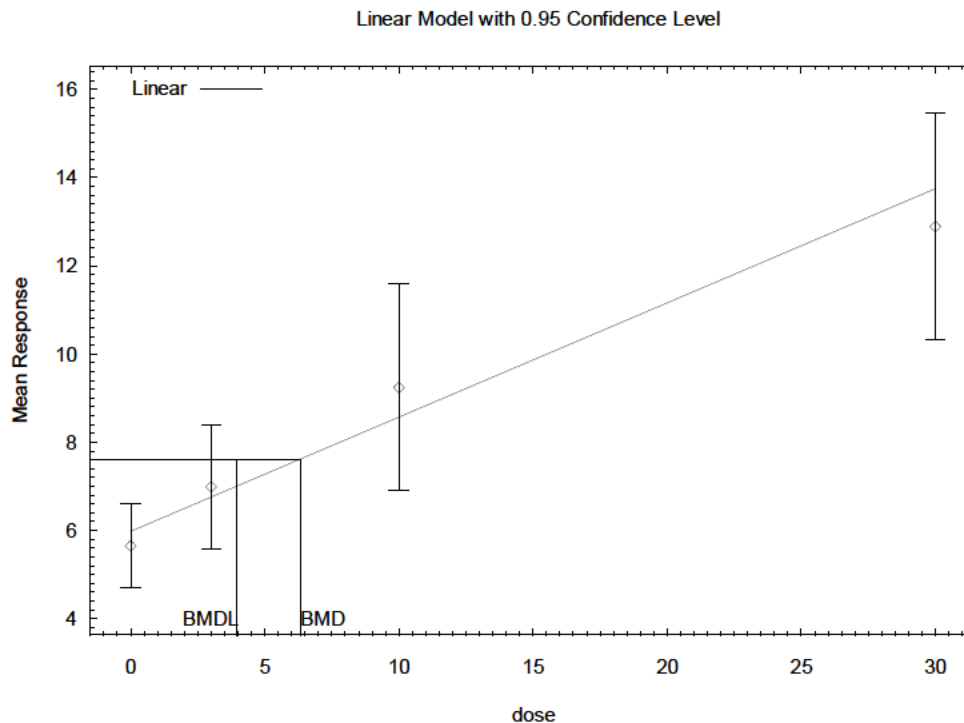
^eNA = degrees of freedom are ≤0; the Chi-Square test for fit is not valid.

AIC = Akaike's Information Criteria; p = p value from the Chi-squared test; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; 1sd = a 1 standard deviation change from the control

Source: Derelanko et al. 1999

APPENDIX A

Figure A-10. Predicted and Observed Changes in Relative Lung Weights in Female Rats Exposed to Basic Chromium Sulfate by Inhalation for 13 Weeks*



14:47 04/17 2008

*BMD=BMC; BMDL=BMCL; BMCs and BMCLs indicated are associated with a 1 standard deviation change from the control, and are in units of mg chromium(III)/m³.

Source: Derelanko et al. 1999

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND**See Sample LSE Table 3-1 (page B-6)**

- (1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

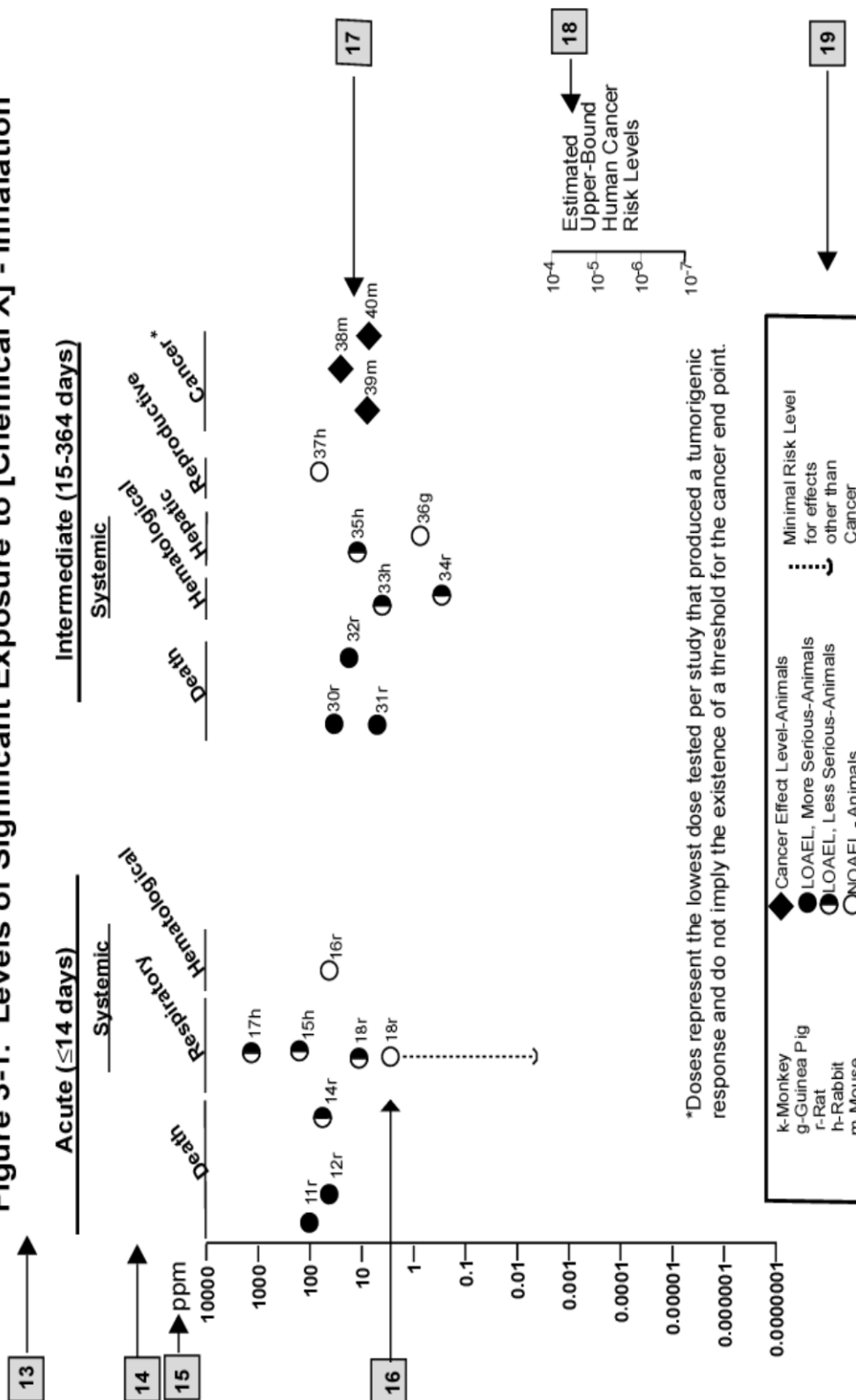
- (13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMDX	dose that produces a X% change in response rate of an adverse effect
BMDLX	95% lower confidence limit on the BMDX
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

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DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
NA/IMDG	North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie

APPENDIX C

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

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OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD ₅₀	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

APPENDIX C

$>$	greater than
\geq	greater than or equal to
$=$	equal to
$<$	less than
\leq	less than or equal to
$\%$	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
$-$	negative
$+$	positive
$(+)$	weakly positive result
$(-)$	weakly negative result

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